DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128123

**WRITTEN REQUEST**

Regeneron Pharmaceuticals, Incorporated
Attention: Usama Aslam, Pharm.D.
Clinical Fellow, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

Dear Dr. Aslam:

Reference is made to your August 21, 2018 Proposed Pediatric Study Request (PPSR) for cemiplimab-rwlc injection.

Reference is also made to our June 30, 2017, inadequate letter regarding the initial PPSR submitted on April 12, 2017.

BACKGROUND:

These studies investigate the potential use of cemiplimab-rwlc in the treatment of pediatric patients with advanced solid tumors as well as pediatric patients with high grade central nervous system tumors, specifically high grade gliomas and diffuse intrinsic pontine gliomas.

Brain tumors are the most common solid pediatric malignancy and result in more deaths than any other pediatric cancer. Diffuse intrinsic pontine gliomas (DIPG) and high-grade gliomas (HGG) account for the majority of these deaths. High-grade gliomas (HGGs) are relatively rare in children, comprising approximately 4% of all brain tumors diagnosed in children age 0-14 and up to 14% in children 10-19 years. Histologically, the vast majority of pediatric HGGs are either anaplastic astrocytomas (WHO grade III) or glioblastomas (WHO grade IV). Diffuse intrinsic gliomas (DIPGs) are gliomas (typically grade II-IV) arising in the brainstem. Even with multi-modality therapies, the 2-year survival for patients with DIPG and HGG is less than 10% and 20%, respectively. The median survival for patients with DIPG and other brainstem HGG remains less than one year. For children older than 3 years of age with HGG, combination therapy with surgical resection, radiation, and chemotherapy remains the standard of care; radiation is typically spared in children younger than 3 years due to the deleterious effects on neurologic development. Surgical resection is not a viable option for patients with DIPG due to the brainstem location and infiltrative nature of the tumor. The use of immunotherapy in treating patients with high grade central nervous system malignancies is an area under study. Evidence of PD-L1 expression on various cancers as well as on tumor-infiltrating immune cells offers a potential pathway that can be targeted with anti-neoplastic immunotherapy. It is notable that studies of other anti-PD-1 or anti-PD-L1 agents have demonstrated limited activity as

monotherapy in pediatric patients with solid tumors. Preclinical data have suggested that radiation "primes" the immune system, as evidenced by increased antigen presentation, increased major histocompatibility complex expression, and increased antigen-specific T-cells in the tumor microenvironment. It has been postulated that hypofractionated radiation may capitalize on these immune stimulating effects. A small group of pediatric patients with recurrent DIPG at the University of California, San Francisco, have been treated with nivolumab combined with reirradiation.

Cemiplimab-rwlc is a human monoclonal antibody directed at PD-1. Cemiplimab-rwlc was approved by FDA on September 28, 2018, for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Cemiplimab-rwlc is being evaluated in several phase 1, 2, and 3 clinical studies in, advanced basal cell carcinoma, advanced cervical cancer, NSCLC, B-cell lymphoma, and other advanced solid malignancies. The safety profile of cemiplimab-rwlc is consistent with that described for other antibodies directed against PD-1. Study R2810-ONC-1423 is an ongoing, first-in-human study of cemiplimab-rwlc as monotherapy and in combination with other anti-cancer therapies in patients with advanced malignancies, including cohorts of adults with Glioblastoma Multiform (GBM). This study contains two dose expansion cohorts with GBM: one cohort of patients with newly diagnosed disease and another with recurrent disease. In these cohorts, patients are treated with one of two doses of Cemiplimab-rwlc (1 mg/kg Q2W or 3 mg/kg Q2W) in combination with hypo-fractionated radiation of 6 Gy x 5 doses. Patients have been treated with the higher dose of 6 mg/kg Q2W in both cohorts.

To obtain needed pediatric information on cemiplimab-rwlc, 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. Pharmacokinetic and safety data in the studies included in this Written Request, supported by data from studies in adults, will be used to establish the dosing and safety of cemiplimab-rwlc in the pediatric patient population.

FDA is not requesting studies in neonates because solid tumors are diagnosed infrequently in the neonatal period. Additionally, when tumors are diagnosed in neonates, they generally do not require chemotherapeutic intervention and are not relapsed or refractory to standard treatments during the neonatal period.

- *Nonclinical study(ies)*: 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 studies:*

  *Study 1:* Study 1 is an open label trial of cemiplimab-rwlc with two phases to determine the safety and recommended phase 2 dose (RP2D) of cemiplimab-rwlc as monotherapy and in combination with radiation therapy (RT). Dose finding will be conducted separately in

patients <12 years of age and ≥ 12 years of age. The study will be conducted through The Pacific Pediatric Neuro Oncology Consortium (PNOC).

- Phase 1: This is a dose-escalation phase to determine the safety, pharmacokinetics, and RP2D of cemiplimab-rwlc monotherapy, with separate cohorts of patients with solid tumors and patients with CNS tumors
- Phase 2: This is an activity-estimating phase with a safety run in to determine the safety and RP2D of cemiplimab-rwlc in combination with radiation, conducted in patients with newly diagnosed DIPG, newly diagnosed HGG, and recurrent HGG

*Study 2:* On the basis of the results of Study 1, FDA and the sponsor will discuss a subsequent study to isolate the contribution of cemiplimab-rwlc. Study 2 may consist of one or more randomized active controlled trial(s) to evaluate the safety and clinical activity of cemiplimab-rwlc in pediatric patients with solid malignant tumors or central nervous system tumors. Specific tumor type(s) to be studied will be selected based on the results of Study 1 and mutually agreed upon by FDA and Regeneron. Elements of study design such as endpoints, choice of comparator, dosage, treatment regimen, sample size, and eligibility criteria will depend on the pediatric tumor(s) chosen for further study. FDA concurrence with the final protocol and statistical analysis plan for Study 2 and any additional studies, if warranted based upon the results of Study 1, will be obtained prior to enrolling the first patient in the study (ies). If the results of Study 1 prove that further studies are not warranted, the sponsor will submit a request for an amendment to the WR.

- *Objective of each study:*

  **Study 1:**

  Phase 1 Primary Objectives:

  - To confirm the safety and anticipated recommended phase 2 dose (RP2D) of cemiplimab-rwlc for children with recurrent or refractory solid or CNS tumors
  - To characterize the pharmacokinetics (PK) of cemiplimab-rwlc given in children with recurrent or refractory solid or CNS tumors

  Phase 1 Secondary and Exploratory Objectives:

  - To assess anti-tumor activity of cemiplimab-rwlc monotherapy as identified by objective response in children with recurrent or refractory solid or CNS tumors
  - To assess immunogenicity

  Phase 2 Primary Objectives:

  - To confirm the safety and anticipated RP2D of cemiplimab-rwlc given concomitantly with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed DIPG

- To confirm the safety and anticipated RP2D of cemiplimab-rwlc given concomitantly with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed HGG
- To confirm the safety and anticipated RP2D of cemiplimab-rwlc given concomitantly with re-irradiation in patients with recurrent HGG
- To assess PK of cemiplimab-rwlc in pediatric patients with newly diagnosed DIPG, newly diagnosed HGG, or recurrent HGG when given in combination with radiation
- To assess anti-tumor activity of cemiplimab-rwlc in combination with radiation in improving overall survival at 12 months (OS12) among patients with newly diagnosed DIPG
- To assess anti-tumor activity of cemiplimab-rwlc in combination with radiation in improving progression-free survival at 12 months (PFS12) among patients with newly diagnosed HGG
- To assess anti-tumor activity of cemiplimab-rwlc in combination with radiation in improving OS12 among patients with recurrent HGG

Phase 2 Secondary Objectives:

- To assess safety and tolerability profiles of cemiplimab-rwlc given in combination with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed DIPG
- To assess safety and tolerability profiles of cemiplimab-rwlc given in combination with conventionally fractionated or hypofractionated radiation among patients with newly diagnosed HGG
- To assess safety and tolerability profiles of cemiplimab-rwlc given in combination with re-irradiation among patients with recurrent HGG
- To assess immunogenicity

**Study 2:**

Primary Objectives:

- FDA concurrence with the final protocol and statistical analysis plan for Study 2 and any additional studies, if warranted based upon the results of Study 1, will be obtained prior to enrolling the first patient in the study(ies).

- ***Patients to be Studied:***

  *Age group in which study(ies) will be performed*:

  **Study 1:**

  - Phase 1: Pediatric patients age 1 month to <18 years of age with recurrent or refractory solid or CNS tumors.

- Enrollment of children less than 1 year of age will occur only once at least 3 children between the ages of ≥ 1 year of age and < 12 years of age have been enrolled and demonstrated tolerability (no DLT) in the DLT period.

- Phase 2: Pediatric patients and young adults ≤ 25 years of age newly diagnosed diffuse intrinsic pontine glioma, newly diagnosed high-grade glioma or recurrent high-grade glioma

**Study 2:** To be agreed upon after completion of Study 1

*Number of patients to be studied:*

**Study 1, Phase 1:** A sufficient number of patients with solid tumors and up to 9 patients with CNS tumors to define the RP2D will be treated in phase 1. This will include at least 6 patients between 1month to <12 years and at least 3 patients between 12 to <18 years.

**Study 1, Phase 2:** A minimum of 100 patients will be enrolled into the efficacy phase

This phase of the study will assess cemiplimab-rwlc combined with radiation in at least 30 patients in an initial 3+3 design, followed by opening of expansion cohorts

- Within the newly diagnosed DIPG Cohort, 40 patients will be randomized 1:1 to either conventionally fractionated radiation or hypofractionated radiation.
- Within the newly diagnosed HGG Cohort, 40 patients will be randomized 1:1 to either conventionally fractionated or hypofractionated radiation.
- Within the recurrent HGG Cohort, approximately 20 total recurrent patients with HGG will be enrolled.

**Study 2:** FDA and the sponsor will reach agreement regarding the number of patients to be studied in further studies, if applicable, after completion of Study1

*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:*

  *Efficacy Endpoints;*

  The primary efficacy endpoint for Study 1 will be overall survival at 12 months (OS12) among patients with DIPG, recurrent HGG and progression-free survival at 12 months (PFS12) among patients with newly-diagnosed HGG. Tumor assessments must be performed every 12 or up to 24 weeks according to Response Assessment in Neuro-Oncology (RANO) criteria or other imaging-based response criteria appropriate for each studied tumor type studied (e.g., Response Evaluation Criteria in Solid Tumors [RECIST] 1.1).

*Safety Endpoints:*

- The primary safety endpoint for Phase 1 of Study 1 is determination of the RP2D of cemiplimab-rwlc for children with recurrent or refractory solid or CNS tumors. The primary safety endpoint for Phase 2 of Study 1 is the determination of the RP2D of cemiplimab-rwlc in combination with radiation in newly-diagnosed DIPG, newly-diagnosed HGG, and recurrent HGG.
- Safety outcomes for Study 1 must include assessment of adverse events (AEs), changes in height, weight, laboratory values and vital signs.
- The following adverse events must be actively monitored in Study 1 and any subsequent studies: infusion reactions, immune-related adverse events, and treatment-emergent cerebral edema.
- Given limited experience with anti-PD-1 or PD-L1 agents in infants, enrollment of children less than 1 year of age will occur only once at least 3 children between the ages of ≥ 1 year of age and < 12 years of age have been enrolled and demonstrated tolerability (no DLT) in the DLT period. The Study team, in conjunction with the Regeneron Safety Monitoring Committee (RSOC) that will include PNOC representation, and the head of safety and clinical development at Regeneron, will conduct a benefit:risk assessment and submit it to the IND prior to the enrollment of patients less than 1 year of age.

*Pharmacokinetic/Pharmacodynamic Endpoints:*

- Estimated cemiplimab-rwlc clearance (CL) and volume of distribution (Vd) from pharmacokinetic samples obtained across all studies from a sufficient number of patients 12 to ≤ 18 years of age and a minimum of 12 patients in the following age groups: 1 month to < 12 years of age. Combine data from all completed studies to develop PK and pharmacodynamic models to explore exposure- response relationships for measures of safety and activity.

- *Known Drug Safety concerns and monitoring:* Safety concerns with administration of cemiplimab-rwlc include immune-mediated toxicities and infusion-related reactions. All clinical studies will include serial clinical and laboratory monitoring for immune toxicities including immune-mediated hepatitis, pneumonitis, colitis, endocrinopathies, nephritis and renal dysfunction. The protocol will contain detailed dose modification and discontinuation instructions, including advice regarding administration of corticosteroids, in the event of expected immune-mediated toxicities.

  An independent Data Safety Monitoring Committee (DSMC) must have oversight over the studies. The DSMC charter will be reviewed prior to study enrollment.

  Based on its mechanism of action, cemiplimab-rwlc may cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential will use effective contraception during treatment with cemiplimab-rwlc and at least 60 days after treatment.

- *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:*

  **Study 1:** For Study 1 and any subsequent studies: cemiplimab-rwlc is supplied as a liquid formulation for intravenous infusion

  Phase 1: The starting cemiplimab-rwlc is 3 mg/kg/dose administered IV every 14 days. Two dose escalation cohorts will be included: patients age 1 month - <12 years of age, and those ages 12 to <18 years. Dose escalation may proceed children to 4.5 mg/kg/dose aged 1 month to 12 years only; for children of all ages may dose de-escalate to a dose of 1 mg/kg/dose. A 3+3 design will be used to determine the RP2D in each age group based on toxicities observed during the first cycle of treatment and PK data.

  Phase 2: cemiplimab-rwlc will be administered at the RP2D for each age group identified in Phase 1 of the study. The initial 3 – 6 patients will be enrolled in a 3+3 design to confirm the dose of cemiplimab-rwlc in combination with radiation.

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

  **Study 1, Phase 1:** Descriptive statistical analyses will be used to describe the safety results for Phase 1.

  **Study 1, Phase 2:**
  The primary efficacy endpoint for the DIPG cohort will be OS12. A minimum of 100 patients will enroll into the Efficacy phase, with 30 patients enrolled in the dose-finding stage to determine the RP2D in combination with radiation, and 20 patients enrolled in each arm of each disease-specific cohort. A total of 40 evaluable DIPG patients treated at the RP2D of cemiplimab-rwlc in combination with radiation will be randomized to each radiation arm (20 DIPG patients each undergoing conventionally fractionated or hypofractionated radiation), a total of 40 evaluable patients with newly diagnosed HGG treated at the RP2D have been randomized to each radiation arm (20 HGG patients each undergoing conventionally fractionated or hypofractionated radiation), and a total of 20 evaluable patients with recurrent HGG treated at the RP2D have been assigned to reirradiation.

  Each DIPG radiation arm will follow a two-stage design where initially 7 patients are entered at the first stage in each arm. If no more than 3 deaths occur within 12 months in the initial cohort, the study will move to the second stage. A total of 20 eligible and evaluable patients will be randomized in order to achieve at least 80% power to detect an

absolute increase of 30% in OS12 within an arm using a one-sided 0.05 level exact binomial test. The arm will be considered a success (reject the associated null hypothesis) if at least 12 of the 20 patients survive beyond 12 months.

The newly-diagnosed HGG cohorts will also follow a two-stage design where initially 7 patients are entered at the first stage. If no more than 2 patients experience disease progression or death within 12 months in the initial cohort, the study will move to the second stage to enroll a total of 20 patients. The null hypothesis for each arm is a PFS12 of 50% with a target alternative hypothesis of 80% PFS12. The target sample size for this cohort is 20 in order to maintain 80% power to detect the alternative hypothesis using a one-sided 0.05 level exact binomial test. The arm will be considered a success (reject the associated null hypothesis) if at least 14 of the 20 patients do not experience disease progression or death at or beyond 12 months.

The recurrent HGG cohort will follow a two-stage design where initially 7 patients are entered at the first stage. If no more than 3 deaths occur within 12 months in the initial cohort, the study will move to the second stage and an additional 13 patients will be entered. The sponsor assumes the OS12 of 40% as null hypothesis and OS12 of 70% as alternative hypothesis. The target sample size for this cohort is 20 eligible patients in order to maintain 80% power to detect the alternative hypothesis using a one-sided 0.05 level exact binomial test. The arm will be considered a success (reject the associated null hypothesis) if at least 12 of the 20 patients survive beyond 12 months

**Study 2:** The statistical analysis plan for Study 2 will be agreed upon with FDA prior to enrollment of the first patient in this study.

- *Pharmacokinetic analysis*

  Population PK analysis should be performed using cemiplimab-rwlc concentration data obtained from all studies. Effect of age and body size on cemiplimab-rwlc lc PK should be assessed. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

- *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 cemiplimab-rwlc is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian,

Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.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 https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before July 31, 2022. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

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 Kristin Jarrell, Pharm.D., Regulatory Health Project Manager, at 301-796-0137.

Sincerely,

*{See appended electronic signature page}*

Gregory Reaman, M.D.
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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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.**

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GREGORY H REAMAN
12/03/2018