BLA 761097
IND 128123

WRITTEN REQUEST

Regeneron Pharmaceuticals, Inc.
Attention: Karen Kuphal, PhD, MBA
Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Dr. Kuphal:

This study investigates the potential use of cemiplimab-rwlc injection 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.

BACKGROUND:

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. HGGs are relatively rare in children, comprising approximately 4% of all brain tumors diagnosed in children ages 0-14 years 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). DIPGs are gliomas arising in the brainstem. Even with multi-modality therapies, the 2-year survival rate 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, with few exceptions. 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.

Cemiplimab-rwlc is a human monoclonal antibody directed at programmed death receptor-1 (PD-1). Cemiplimab-rwlc has been approved by FDA 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 and the treatment of patients with locally advanced or metastatic basal cell carcinoma who have been previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate. It is also approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) or locally advanced NSCLC, as monotherapy in patients whose tumors have high (tumor proportion score [TPS] ≥50%) PD-L1 expression and combined with chemotherapy in patients with any PD-L1 expression. The safety profile of cemiplimab-rwlc is consistent with that described for other antibodies directed against PD-1.

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.

To obtain needed pediatric information on cemiplimab-rwlc injection, 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), that you submit information from the studies described below. Pharmacokinetic and safety data in the study 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. Although the use of similar in-class products in pediatric patients has been studied in recent years and more scientific information has become available in the literature, there is a lack of information in pediatric patients with CNS tumors. This study is specifically designed to assess the safety and effectiveness of cemiplimab-rwlc in, among other things, pediatric patients with CNS tumors, which is a unique characteristic of this study.

FDA is not requesting studies in neonates because CNS tumors are diagnosed infrequently in the neonatal period. Additionally, when CNS tumors are diagnosed in neonates, they typically do not become relapsed or refractory to standard treatments during the neonatal period.

- *Nonclinical study(ies)*:

Based on review of the available nonclinical toxicology data, 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). This study will be conducted in 2 phases:

  - 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 Objectives:*
  Phase 1 Primary Objectives:

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

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

- *Patients to be Studied:*
  - *Age groups to be studied:*
    - Phase 1: Pediatric patients birth 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 after at least 3 children between the ages of ≥ 1 year of age and < 12 years of age have been enrolled
    - Phase 2: Pediatric patients and young adults ≤ 25 years of age with newly diagnosed DIPG, newly diagnosed HGG or recurrent HGG
  - *Number of patients to be studied:*
    - Phase 1: A sufficient number of patients with solid tumors and a minimum of 9 patients with CNS tumors. This will include at least 6 patients between birth to < 12 years of age and at least 3 patients between 12 to < 18 years of age.
    - Phase 2: If futility criteria are not met, then a minimum of 100 patients will be enrolled into the efficacy phase as follows:
      - Within the newly diagnosed DIPG Cohort, approximately 40 patients will be randomized 1:1 to either

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

- *Study endpoints:*

  ☐ Pharmacokinetic/Pharmacodynamic endpoints: Estimated cemiplimab-rwlc clearance (CL) and volume of distribution (Vd) from pharmacokinetic samples obtained from a sufficient number of patients 12 to ≤ 18 years of age and a minimum of 12 patients birth to < 12 years of age.

  ☐ Primary efficacy endpoint(s): The primary efficacy endpoint for Study 1 is overall survival at 12 months (OS12) in patients with DIPG and recurrent HGG; progression-free survival at 12 months (PFS12) in patients with newly-diagnosed HGG. Tumor assessments must be performed approximately every 12 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/Monitoring:*

  ☐ The primary safety endpoint for the Phase 1 portion of Study 1 is determination of the RP2D of cemiplimab-rwlc for pediatric patients with recurrent or refractory solid or CNS tumors. The primary safety endpoint for the Phase 2 portion 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 will be monitored in Study 1: infusion reactions, immune-mediated adverse events, and neurological toxicities, including cerebral edema.
  ☐ Enrollment of children less than 1 year of age will occur only after 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 safety monitoring team with PNOC will conduct a benefit:risk assessment and submit it to the IND prior to the enrollment of patients less than 1 year of age.

The protocol must specify monitoring of adverse events until symptom resolution or until the condition stabilizes.

- *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 contains detailed dose modification and discontinuation instructions, including advice regarding administration of corticosteroids, in the event of expected immune-mediated toxicities.

  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.

- *A Data Safety Monitoring Committee (DSMC) must be included for all studies.*

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

Study 1, Phase 1: Descriptive analyses of safety results will be performed.

Study 1, Phase 2: Descriptive analyses of safety and efficacy results will be performed. A minimum of 100 patients will enroll into the efficacy phase if futility criteria are not met.

The DIPG cohorts will follow a two-stage design and will randomize patients with newly diagnosed DIPG to receive cemiplimab-rwlc at the RP2D in combination with radiation, approximately 20 to the conventionally fractionated radiation arm and approximately 20 to the hypofractionated radiation arm (if both stages of the trial proceed). Approximately seven patients will initially be randomized to each arm during the first stage. If no more than 3 deaths occur within 12 months in the initial cohort, the arm will move to the second stage and enroll approximately 13 additional patients to the arm 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; otherwise, the arm will be closed to enrollment. The arm will be considered a success (i.e., the null hypothesis will be rejected) if at least 12 of 20 patients in the arm survive longer than 12 months.

The newly-diagnosed HGG cohorts will also follow a two-stage design and will randomize patients with newly diagnosed HGG to receive cemiplimab-rwlc at the RP2D in combination with radiation, approximately 20 to the conventionally fractionated radiation arm and approximately 20 to the hypofractionated radiation arm (if both stages of the trial proceed). Approximately 7 patients will initially be randomized to each arm during the first stage. If no more than 2 patients experience disease progression or death within 12 months in the initial cohort, the arm will move to the second stage to enroll approximately 13 additional patients to the arm, for a total of approximately 20 patients in each arm. The null hypothesis for each arm is a PFS12 of 50% with a target alternative hypothesis of 80% PFS12. The target sample size for each arm 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 (i.e., the null hypothesis will be rejected) 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 approximately 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 approximately 13 additional patients will be entered. Assuming an OS12 of 40% as the null hypothesis and an OS12 of 70% as the alternative hypothesis, the target sample size of 20 eligible patients maintain provides 80% power to detect the alternative hypothesis using a one-sided 0.05 level exact binomial test. The arm will be considered a success (i.e., the null hypothesis will be rejected) if at least 12 of the 20 patients survive beyond 12 months.

- Pharmacokinetic analysis

  Population PK analyses should be performed using cemiplimab-rwlc concentration data obtained from Study 1. Effect of age and body weight on cemiplimab-rwlc PK should be assessed. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored if warranted.

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.

- *Biologic product information:*

  - *Dosage form:* liquid formulation
  - *Route of administration:* intravenous infusion
  - *Regimen:*
    - *Phase 1*: The starting dosage of cemiplimab-rwlc is 3 mg/kg/dose administered IV every 14 days. Cemiplimab-rwlc dosage will be evaluated in two cohorts based on patient age: a cohort of patients birth to < 12 years of age, and a cohort of patients 12 to < 18 years of age. 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. Based on this design, dose escalation may proceed to the 4.5 mg/kg/dose level in the birth to 12 years of age cohort only; patients in the 12 to < 18 years of age cohort may not escalate beyond the 3 mg/kg/dose. If warranted, a dose level of 1 mg/kg/dose may be evaluated in either or both cohorts.
    - Phase 2: Cemiplimab-rwlc will be administered at the RP2D for each age group identified in Phase 1 of the study. The initial 3 to 6 patients in each cohort will be enrolled in a 3+3 design to confirm the safety of the dose of cemiplimab-rwlc in combination with radiation.

  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 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 600.80 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.[1] 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 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 April 30, 2025. Please keep in mind that pediatric exclusivity can only attach to existing exclusivity, if any, 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.

  If FDA has not determined whether cemiplimab-rwlc is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

- *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.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.fda.gov/media/154109/download

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 Biologics License Application (BLA) or as a supplement to your approved BLA 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 FD&C 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.[3]

If you wish to discuss any amendments to this Written Request, submit your proposed changes using strikethrough and underline (Text added is underlined. Text deleted is strikethrough.) 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 PHS Act, you are required to comply with the provisions of section

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

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 on the Clinical Trials website.[4]

If you have any questions, contact Jeffrey Ingalls, Senior Regulatory Project Manager, at Jeffrey.Ingalls@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Acting Associate Director, Pediatric Oncology
Office of Oncological Diseases
Center for Drug Evaluation and Research

[4] www.ClinicalTrials.gov

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/

MARTHA B DONOGHUE
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