DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

BLA ACCELERATED APPROVAL

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director
Global Regulatory Affairs, Immuno-Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Pappalardo:

Please refer to your Biologics License Application (BLA) dated and received September 23, 2016, submitted under section 351 of the Public Health Service Act for Bavencio (avelumab) Injection, for intravenous use, 20 mg/mL.

LICENSING

We have approved your BLA for Bavencio (avelumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Bavencio under your existing Department of Health and Human Services U.S. License No. 1773. Bavencio is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture avelumab drug substance at Merck Serono S.A. in Corsier-sur-Vevey, Switzerland. The final formulated product will be manufactured, filled, labeled, and packaged at Merck Serono S.A. in Aubonne, Switzerland. You may label your product with the proprietary name Bavencio and will market it at 200 mg/10 mL in a single dose vial.

DATING PERIOD

The dating period for Bavencio shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Bavencio to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Bavencio, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton label submitted on February 24, 2017, and immediate container label submitted on February 10, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and**

Container Labels for approved BLA 761049." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Bavencio was not referred to an FDA advisory committee because this biologic is not the first in its class.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated March 20, 2017. This requirement, along with required completion dates, is listed below.

3185-1 Conduct and submit the results of a multicenter clinical trial confirming the clinical benefit of avelumab in patients with metastatic Merkel cell carcinoma (MCC) who have not received prior systemic therapies for metastatic MCC. The trial will enroll at least 100 patients followed for a minimum of 12 months, in order to establish the objective response rate and characterize the durability of response for first-line treatment of metastatic MCC. All patients will be followed for overall survival until at least 70% of patients have died in order to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided.

Trial Completion:	June 2026
Final Report Submission:	December 2026

We acknowledge submission of the final clinical protocol to IND 119394 on October 26, 2016. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of immune mediated adverse reactions in pediatric patients ages 12 to 18 years.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of immune mediated adverse reactions in pediatric patients.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

3185-2 Conduct a trial in a sufficient number of pediatric patients ages 12-18 to adequately characterize baseline risk factors, safety outcomes, and clinical responses following exposure to avelumab.

The timetable you submitted on March 21, 2017, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	October 2017
Interim Report Submission:	October 2018
Interim Report Submission:	October 2019
Interim Report Submission:	October 2020
Interim Report Submission:	October 2021

Trial Completion: October 2022
Final Report Submission: June 2023

Submit the clinical protocol to your IND 119394 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all interim and final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70 . We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3185-3 Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (including an updated cutpoint for the screening and confirmatory ADA assays and for the neutralizing assay as requested in 3185-5) capable of sensitively detecting ADA responses in the presence of avelumab levels that are expected to be present in the serum at the time of patient sampling. The incidence of treatment-emergent ADA responses will be evaluated in at least 300 avelumab-treated patients. The final report will include information on the level of avelumab in each patient's test sample at each sampling point with an appropriate cutpoint.

The timetable you submitted on February 20, 2017, states that you will conduct this trial according to the following schedule:

Final Report Submission: August 2017

3185-4 Conduct an animal study that will measure the effect of PD-L1 inhibition on the magnitude of the primary (1st vaccination) and recall (2nd vaccination) antibody responses to antigen challenge (e.g. KLH). This study will evaluate the effect of PD-L1 inhibition on the primary immune response once steady state plasma levels have been achieved and will reassess the magnitude of the recall response after a suitable period in the presence or absence of continued dosing. The study should include, if possible, an evaluation of cytokine production by T cells at appropriate timepoints.

The timetable you submitted on February 20, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2017
Study Completion:	October 2017
Final Report Submission:	January 2018

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3185-5 Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against avelumab in the presence of avelumab levels that are expected to be present in samples at the time of patient sampling. Patient samples should be banked for storage until the improved method is available.

The timetable you submitted on February 20, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2017

3185-6 Implement the performance at least one media fill run per year which incorporates both the maximum sterile hold time after filtration and the maximum filing time starting from 2017. Submit the information and summary data from the first 2017 media fill as a post marketing commitment in accordance with 21 CFR 601.12.

The timetable you submitted on February 20, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2018

Submit clinical protocols to your IND 119394 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA.

In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved prescribing information (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn

from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Idara Udoh, Senior Regulatory Health Project Manager, at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
03/23/2017