

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761049Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

BLA#: 761049 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: DOP2 PDUFA Goal Date: May 23, 2017 Stamp Date: September 23, 2016

Proprietary Name: Bavencio

Established/Generic Name: avelumab

Dosage Form: injection, 200 mg/10 mL (20 mg/mL) solution in single dose vial

Applicant/Sponsor: EMD Serono, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Bavencio is a programmed death ligand -1 (PD-L1) blocking antibody indicated for the treatment of patients with metastatic Merkel cell carcinoma.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- ☐ Yes. Please proceed to Section D.
- ☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- ☒ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

☐ Disease/condition does not exist in children

☐ Too few children with disease/condition to study

☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

/s/

IDARA UDOH
02/23/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
BLA # 761049	BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A (an action package is not required for SE8 or SE9 supplements)
Proprietary Name: Bavencio Established/Proper Name: avelumab Dosage Form: for intravenous use, 20 mg/mL		Applicant: EMD Serono, Inc. Agent for Applicant (if applicable): N/A
RPM: Idara Udoh		Division: DOP2
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☒ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☐ No changes ☐ New patent/exclusivity (notify CDER OND IO) Date of check: <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>May 23, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions (specify type and date for each action taken)		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☒ Received (on 3/8/2017, by OPDP)
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☒ Fast Track	☐ Rx-to-OTC full switch
☒ Rolling Review	☐ Rx-to-OTC partial switch
☒ Orphan drug designation	☐ Direct-to-OTC
☒ Breakthrough Therapy designation	

**(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))**

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☒ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☒ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other: ASCO Burst and Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters

- ❖ Copies of all action letters (*including approval letter with final labeling*)

Action and date: BLA Accelerated Approval issued on 3/23/2017

Labeling

- ❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

- Most recent draft labeling (*if it is division-proposed labeling, it should be in track-changes format*)
- Original applicant-proposed labeling

☒ Included
Final PI received 3/23/2017
☒ Included
Original PI received 9/23/2016

- ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (*write submission/communication date at upper right of first page of each piece*)

- Most-recent draft labeling (*if it is division-proposed labeling, it should be in track-changes format*)
- Original applicant-proposed labeling

☒ Medication Guide
☐ Patient Package Insert
☐ Instructions for Use
☐ Device Labeling
☐ None
☒ Included
Final Medication Guide received 3/22/2017
☒ Included
Original Medication Guide received 9/23/2016

- ❖ Labels (**full color** carton and immediate-container labels) (*write submission/communication date on upper right of first page of each submission*)

- Most-recent draft labeling

☒ Included
Final Carton Label received 2/24/2017
Final Container Label received 2/10/2017

- ❖ Proprietary Name
- Acceptability/non-acceptability letter(s) (*indicate date(s)*)
 - Review(s) (*indicate date(s)*)

Letters

- Conditional Acceptance issued 10/28/2016
- Acknowledgment issued 10/12/2016

Reviews
Reviewer Signed 10/26/2016; TL Concurred 10/26/2016

- ❖ Labeling reviews (*indicate dates of reviews*)

RPM: None

- DMEPA: ☒ Additional reviews 3/2/2017 and 3/1/2017; initial review signed 1/6/2017
- DMPP/PLT (DRISK): ☒ review 2/21/2017
- OPDP: ☒ review of PI 2/16/2017
- SEALD: None
- CSS: None
- Product Quality ☒ reviewer signed 3/9/2017; concurrence 3/9/2017

	Other: ☒ See Clinical, Nonclinical, Clinical Pharmacology, and Statistics sections for dates
Administrative / Regulatory Documents	
❖ RPM Filing Review⁴/Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	11/22/2016 final review; 11/22/2016 CPMS concurrence ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	N/A
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>orphan drug designation granted on September 21, 2015 (designation 15-4918), therefore exempt from PREA</u>	Pediatric page uploaded 2/23/2017
❖ Breakthrough Therapy Designation	☐ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	Breakthrough Therapy Designation granted 11/17/2015
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	Generated 11/18/2015 Division Director concurrence 11/19/2015
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (completed CDERMPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)	N/A
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	Clinical 3/23/2017 Clinical 3/22/2017 Proposed PMR/PMC 3/21/2017 PI Edits 3/14/2017 Proposed PMR/PMC 3/14/2017 Clinical/PI Edits 3/6/2017 (uploaded 3/14/2017) PI Edits 3/3/2017 (uploaded 3/14/2017) Clinical 2/24/2017 (uploaded 3/1/2017) Carton/Container Edits

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

	2/23/2017 Late Cycle Background Package 2/17/2017 Proposed PMR/PMC 2/17/2017 CMC 2/14/2017 PI Edits 2/10/2017 Clinical 2/9/2017 CMC 2/7/2017 Clinical 2/6/2017 Carton/Container Edits 2/1/2017 CMC 2/1/2017 Clinical 2/1/2017 (uploaded 2/2/2017) Clinical 1/30/2017 Clinical Pharmacology 1/27/2017 (uploaded 1/30/2017) Clinical 1/26/2017 Clinical 1/24/2017 Clinical 1/18/2017 CMC 1/13/2017 CMC 1/4/2017 Clinical 12/16/2016 CMC 12/15/2016 Clinical 12/5/2016 CMC 11/30/2016 Filing Review Issue Identified 11/22/2016 CMC 11/29/2016 Clinical 11/15/2016 Clinical 11/8/2016 (uploaded 11/15/2016) CMC 11/2/2016 Pharmacovigilance 10/20/2016 (uploaded 11/3/2016) OSI 10/18/2016 (uploaded 11/3/2016) QT IRT 10/18/2016 (uploaded 11/3/2016) OSI 10/16/2016 (uploaded 11/3/2016) Clinical 10/14/2016 (uploaded 11/3/2016) Clinical Pharmacology 10/14/2016 (uploaded 11/3/2016) QT IRT 9/23/2016 (uploaded 11/3/2016) BLA Acknowledgment 10/14/2016 BLA Acknowledge Pre- submission 9/14/2016 BLA Acknowledge Pre- submission 7/18/2016

❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Sponsor TCON to Discuss PI: 3/20/2017 Sponsor TCON to Discuss PI: 3/14/2017 Sponsor TCON to Discuss PI: 3/6/2017 Team Meeting #2, 2/24/2017 Team Meeting #1, 2/7/2017 • Held 12/8/2016; Midcycle Meeting Summary, uploaded 1/6/2017 • Division Director Priority Review Memo 11/29/2016 • Held 11/8/2016; Filing Meeting Memo attached to RPM Filing Review, uploaded 11/22/2016 • Held 10/17/2016; Planning Meeting Summary, uploaded 11/4/2016
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	6/16/2017; minutes uploaded 7/6/2016
• EOP2 meeting (<i>indicate date of mtg</i>)	N/A
• Mid-cycle Communication (<i>indicate date of mtg</i>)	1/5/2017 meeting; minutes uploaded 1/30/2017
• Late-cycle Meeting (<i>indicate date of mtg</i>)	2/27/2017 meeting; minutes uploaded 3/21/2017
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	• 9/2/2016 Guidance (EMA); minutes uploaded 9/7/2016 • 6/8/2016 nonclinical WRO • 4/26/2016 CMC meeting; minutes uploaded 5/24/2016 • 4/15/2016 clinical pharmacology meeting; minutes issued 4/18/2016 • 2/2/2016 Initial Comp Multidiscip BTD meeting; minutes issued 2/10/2016
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	No separate review; 3/23/2017 Final review, see Multidisciplinary Review
Division Director Summary Review (<i>indicate date for each review</i>)	N/A
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☒ None Included in Office Director Decisional Memo
PMR/PMC Development Templates (<i>indicate total number</i>): 6 (2 CMC development templates not included in action package)	• Clinical PMR 3/23/2017, Safety Director concurrence 3/23/2017

	- Clinical Pharmacology PMC 3/22/2017, Safety Director concurrence 3/23/2017 - Nonclinical PMC 3/21/2017, Safety Director concurrence 3/21/2017 - Clinical PMR 3/20/2017, Safety Director concurrence 3/20/2017 - CMC PMC - CMC/Microbiology PMC
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
• Clinical review(s) (indicate date for each review)	Primary review and concurrence 2/23/2017 Filing review signed 11/14/2016
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (indicate date of review/memo)	Financial disclosure addressed in 11/14/2016 filing review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	Final review 2/21/2017; concurrence 2/21/2017
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	<u>Letters</u> VAI letters to Bhatia 3/28/2017 VAI letters to Shih 3/28/2017 Final review and concurrence 2/17/2017
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	Primary review and concurrence 2/23/2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

	Filing review and concurrence 11/21/2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	Final review and concurrence 2/21/2017 Final QT IRT review and concurrence 12/12/2016 Filing review and concurrence 11/10/2016
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Final review and concurrence 2/23/2017 Filing review 11/8/2016, concurrence 11/14/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☐ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	Primary/secondary review signed 2/17/2017 Filing review signed 10/31/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date) (all original applications and all efficacy supplements that could increase the patient population)	See 2/17/2017 IQA for information on categorical exclusion
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change))	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	N/A
• Finalize 505(b)(2) assessment	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☒ Done (Send email to CDER OND IO)
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 14, 2017

From: Idara Udoh, MS, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: BLA761049: Sponsor Teleconference to Discuss 3/7/2017 EMD Serono Revisions to Package Insert

EMD Serono Attendees:

Glen Andrews, Pfizer Immuno-oncology Asset Team Leader
Kevin Chin, Global Clinical Development
Gulseren Guzel, Global Drug Safety
Melissa Hennessy, Global Clinical Development
Jacques Mascaro, Head, Global Regulatory Affairs
Virginia Pappalardo, Global Regulatory Affairs Lead
Alise Reicin, Head, Global Clinical Development
Philippe Serrano, Global Regulatory Affairs
Kamal Shah, Global Drug Safety
Jennifer Stevens, Global Regulatory Affairs
Laurie Strawn, Pfizer GRA Portfolio Lead Immuno-Oncology/GU Malignancies
Anja Von Heydebreck, Global Biostatistics
Christian Wrehlke, GRA Labeling

FDA Attendees:

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)
Suzanne Demko, BLA 761049 Cross-Discipline Team Leader, DOP2
Denise Casey, Clinical Reviewer, DOP2
Idara Udoh, Senior Regulatory Health Project Manager, DOP2
Ann Marie Trentacosti, Patient Labeling Team

Discussion:

The purpose of the teleconference was to discuss EMD Serono's edits made to the Bavencio (avelumab) package insert (PI) and Medication Guide, received March 7, 2017, following agreements reached during the March 6, 2017 teleconference. The following sections of the PI were addressed:

- Highlights
 - Indications and Usage: Revision of indication statement from “(b) (4)” to “pediatric patients 12 years and older” in indication statement
 - Dosage and Administration: addition of “with acetaminophen and an antihistamine” to provide important information for prescribers
 - Warnings and Precautions: Language revised for consistency; deletion of nonessential text
- Section 1 (Indications and Usage)

- o Revision of indication statement from “(b) (4)” to “pediatric patients 12 years and older”. (b) (4)
- Section 2 (Dosage and Administration)
 - o 2.3 Dose Modifications, Table 1: Addition and deletion of text within table, with comments
 - o 2.4 Preparation and Administration: Formatting comments and deletion of unnecessary test
- Section 5 (Warnings and Precautions)
 - o Subsections 5.1-5.7: Addition of cross reference to section 6.1, which provides definition of immune-mediated adverse events
 - o 5.2, 5.3, 5.7: Deletion of text addressing (b) (4), with comment; minor revisions
 - o 5.4-5.6: Minor revisions, language revised for clarity, FDA comments
- Section 6 (Adverse Reactions)
 - o Language revised for clarity, deletion of language found not useful for prescribers, grammatical and formatting edits
- Section 8 (Use in Specific Populations)
 - o 8.4 Pediatric Use: Revision to support expansion of pediatric patients in indication. (b) (4)
- Section 14 (Clinical Studies)
 - o Addition of trial identifier

EMD Serono acknowledged FDA’s edits and comments and agreed to submit a revised PI by March 16, 2017.

The call ended.

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/s/

IDARA UDOH
04/05/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 20, 2017

From: Idara Udoh, MS, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: BLA761049: Sponsor Teleconference to Discuss 3/6/2017 EMD Serono Revisions to Package Insert and Medication Guide, in Response to 3/3/2017 FDA Information Request

EMD Serono Attendees:

Glen Andrews, Pfizer Immuno-oncology Asset Team Leader
Kevin Chin, Global Clinical Development
Dietmar Gross, Head, Global Early Development
Gulseren Guzel, Global Drug Safety
Melissa Hennessy, Global Clinical Development
Steven Hildemann, Chief Medical Officer, Head Global Medical Affairs and Global Drug Safety
Helga Koch, Global Drug Safety
Jacques Mascaro, Head, Global Regulatory Affairs
Virginia Pappalardo, Global Regulatory Affairs Lead
Alise Reicin, Head, Global Clinical Development
Philippe Serrano, Global Regulatory Affairs
Kamal Shah, Global Drug Safety
Jennifer Stevens, Global Regulatory Affairs
Laurie Strawn, Pfizer GRA Portfolio Lead Immuno-Oncology/GU Malignancies
Christine Vidsens, GRA Promotional Materials
Christian Wrehlke, GRA Labeling

FDA Attendees:

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)
Suzanne Demko, BLA 761049 Cross-Discipline Team Leader, DOP2
Denise Casey, Clinical Reviewer, DOP2
Idara Udoh, Senior Regulatory Health Project Manager, DOP2

Discussion:

The purpose of the teleconference was to discuss EMD Serono's edits made to the Bavencio (avelumab) package insert (PI) and Medication Guide, received March 6, 2017, in response to March 3, 2017 FDA information request containing PI and Medication Guide comments and revisions. The following sections of the PI were addressed:

- Highlights
 - Indications and Usage, Dosage and Administration: FDA comment regarding pediatric population in indication statement.
- Section 1 (Indications and Usage)
 - FDA comment regarding pediatric population in indication statement.

- Section 8 (Use in Specific Populations)
 - 8.4 Pediatric Use: FDA comment regarding pediatric population in indication statement. Proposed language regarding safety and effectiveness of drug in pediatric patients, for EMD Serono consideration.

FDA also informed EMD Serono that proposed PMR language subject to the reporting requirements of section 505(o) was forthcoming, and that EMD Serono should provide milestone completion dates.

EMD Serono acknowledged FDA's edits and comments and agreed to submit a revised PI and Medication Guide by COB March 21, 2017.

The call ended.

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/s/

IDARA UDOH
04/05/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 6, 2017

From: Idara Udoh, MS, Sr. Regulatory Health Project Manager DOP2/OHOP

Subject: BLA761049: Sponsor Teleconference to Discuss 3/6/2017 EMD Serono Revisions to Package Insert and Medication Guide, in Response to 3/3/2017 FDA Information Request

EMD Serono Attendees:

Glen Andrews, Pfizer Immuno-oncology Asset Team Leader
Kevin Chin, Global Clinical Development
Dietmar Gross, Head, Global Early Development
Gulseren Guzel, Global Drug Safety
Melissa Hennessy, Global Clinical Development
Steven Hildemann, Chief Medical Officer, Head Global Medical Affairs and Global Drug Safety
Helga Koch, Global Drug Safety
Jacques Mascaro, Head, Global Regulatory Affairs
Virginia Pappalardo, Global Regulatory Affairs Lead
Alise Reicin, Head, Global Clinical Development
Philippe Serrano, Global Regulatory Affairs
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Jennifer Stevens, Global Regulatory Affairs
Laurie Strawn, Pfizer GRA Portfolio Lead Immuno-Oncology/GU Malignancies
Christine Vidsens, GRA Promotional Materials
Christian Wrehlke, GRA Labeling

FDA Attendees:

Patricia Keegan, Director, Division of Oncology Products 2 (DOP2)
Suzanne Demko, BLA 761049 Cross-Discipline Team Leader, DOP2
Denise Casey, Clinical Reviewer, DOP2
Idara Udoh, Senior Regulatory Health Project Manager, DOP2
Ann Marie Trentacosti, Patient Labeling Team

Discussion:

The purpose of the teleconference was to discuss EMD Serono's edits made to the Bavencio (avelumab) package insert (PI) and Medication Guide, received March 6, 2017, in response to March 3, 2017 FDA information request containing PI and Medication Guide comments and revisions. The following sections of the PI were addressed:

- Highlights
 - Indications and Usage, Dosage and Administration: Fix formatting
 - Warnings and Precautions: Request to harmonize with remainder of PI addressing respective sections; formatting and grammatical edits

- Section 1 (Indications and Usage)
 - Addition of “(b) (4)” patients to indication statement, consistent with current FDA practice.
- Section 2 (Dosage and Administration)
 - 2.3 Dose Modifications, Table 1: Addition and deletion of text within table, with comments
- Section 5 (Warnings and Precautions)
 - Subsections 5.2- 5.5, 5.7: Minor edits
- Section 6 (Adverse Reactions)
 - Addition of serious adverse events
 - Table 2: Minor edits
- Section 8 (Use in Specific Populations)
 - 8.4 Pediatric Use: Revision to support expansion of pediatric patients in indication. (b) (4)
- Section 11 (Description)
 - Deletion of “(b) (4)” in line 398
- Section 13 (Nonclinical Toxicology)
 - Addition of section 13.2

FDA provided edits to the Medication Guide, as needed, and provided rationale for the edits.

EMD Serono acknowledged FDA’s edits and comments and agreed to submit a revised PI and Medication Guide by March 7, 2017.

The call ended.

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/s/

IDARA UDOH
04/05/2017

Team Meeting Summary
February 24, 2017

BLA: 761049, Type 1 New Molecular Entity

Rolling Submission:

- **Nonclinical eCTD submission—SDN 1 (received July 6, 2016)**
- **CMC eCTD submission—SDN 3 (received September 2, 2016)**
- **Clinical eCTD submission—SDN 4 (received September 23, 2016)**

Product: avelumab (MSB0010718C), injection for intravenous use, 20 mg/mL
Proposed Proprietary Name: Bavencio
Submission Date: September 23, 2016
Received Date: September 23, 2016
Sponsor: EMD Serono, Inc.

Proposed Indication: Treatment of patients with metastatic Merkel Cell Carcinoma

Review Team: Office Signatory—Richard Pazdur; Division Signatory—Patricia Keegan

Project Management

Monica Hughes, CPMS
Idara Udoh, Sr. Regulatory
Project Manager (RPM)

Clinical

Suzanne Demko, Clinical Team
Leader
Denise Casey, Clinical
Reviewer

Nonclinical

Whitney Helms, Non-Clinical
TL
Alexander Putman, Non-
Clinical Reviewer

Clinical Pharmacology

Jeanne Fourie-Zirkelback, Clin
Pharm TL
Safaa Burns, Clin Pharm
Reviewer

Pharmacometric

Jiang Liu, TL
Nan Zheng, Reviewer

Genomics

Rosane Charlab Orbach

Biometrics

Kun He, Biometrics TL
Pallavi Mishra-Kalyani,
Biometrics Reviewer

Product Quality (OBP)

Truong Quach, Regulatory
Business Project Manager
Joel Welch, OBP-ATL
Arulvathani Arudchandran,
OBP Reviewer
Maria Reyes Candau-Chacon,
DMA-DS
Lakshmi Narashmhan, DMA-
DP
Colleen Thomas, DMA-QAL
Steven Fong, Facilities
Reviewer, DIA

Labeling

Anne Marie Trentacosti,

1. Updates

- a. Early action date (March 23, 2017), as discussed during February 7, 2017 team meeting
- b. Primary reviews completed by clinical, statistics, nonclinical, clinical pharmacology, and CMC
- c. Consult reviews completed by PLT, OPDP, Risk Management, and OSI
- d. Carton and container label
 - i. Information requests sent 2/2 (both; response received 2/17) and 2/23 (carton; response received 2/24)
- e. Medication Guide
 - i. PLT provided comments on 2/21 and clinical provided additional comments on 2/23
- f. Package Insert Label
 - i. Proposed comments issued on 2/10, and responses received on 2/20
 - ii. EMD Serono informed RPM of discrepancies in 2/20 PI submission, and resubmitted PI with corrections to section Highlights section, and sections 5.7, 6.1, and 14
- g. PMR/PMC language
 - i. Proposed language to clinical (PMR), nonclinical (PMC), clinical pharmacology (PMC), and CMC (PMC) sent to Sponsor on 2/17; responses and milestone completion dates received 2/20 and forwarded to Dr. Summers for review
- h. Bavencio Multidisciplinary Review
 - i. All sections to be completed by 3/1
- i. Press Release and Burst
 - i. Draft language sent to Clinical and DD, under review

2. Review of Package Insert and Medication Guide

- a. Indication statement to include adult and adolescent patients
 - i. Clinical to provide additional edits; package insert and Medication Guide to be forwarded to EMD Serono by next week.
- b. CMC labeling reviewer accepted EMD Serono's response to both carton and container labels

3. Additional Items:

- a. Tentatively scheduled meetings: 3/1 pre-LCM; 3/6 Team meeting (repurpose for labeling negotiations?)

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/s/

IDARA UDOH
04/05/2017

Team Meeting Summary
February 7, 2017

BLA: 761049, Type 1 New Molecular Entity

Rolling Submission:

- **Nonclinical eCTD submission—SDN 1 (received July 6, 2016)**
- **CMC eCTD submission—SDN 3 (received September 2, 2016)**
- **Clinical eCTD submission—SDN 4 (received September 23, 2016)**

Product: avelumab (MSB0010718C), injection for intravenous use, 20 mg/mL
Proposed Proprietary Name: Bavencio
Submission Date: September 23, 2016
Received Date: September 23, 2016
Sponsor: EMD Serono, Inc.

Proposed Indication: Treatment of patients with metastatic Merkel Cell Carcinoma

Review Team: Office Signatory—Richard Pazdur; Division Signatory—Patricia Keegan

Project Management

Monica Hughes, CPMS
Idara Udoh, Sr. Regulatory
Project Manager (RPM)

Clinical

Suzanne Demko, Clinical Team
Leader
Denise Casey, Clinical
Reviewer

Nonclinical

Whitney Helms, Non-Clinical
TL
Alexander Putman, Non-
Clinical Reviewer

Clinical Pharmacology

Jeanne Fourie-Zirkelback, Clin
Pharm TL
Safaa Burns, Clin Pharm
Reviewer

Pharmacometric

Jiang Liu, TL

Nan Zheng, Reviewer

QT IRT

Janell Chen
Michael Li

Genomics

Rosane Charlab Orbach

Biometrics

Kun He, Biometrics TL
Pallavi Mishra-Kalyani,
Biometrics Reviewer

Product Quality (OBP)

Truong Quach, Regulatory
Business Project Manager
Joel Welch, OBP-ATL
Arulvathani Arudchandran,
OBP Reviewer
Maria Reyes Candau-Chacon,
DMA-DS
Lakshmi Narashmhan, DMA-
DP

Colleen Thomas, DMA-QAL
Steven Fong, Facilities
Reviewer, DIA

OSE

Latonia Ford, Safety RPM
DMEPA: Janine Stewart,
Medication Error
Reviewer
DMEPA: Alice Chi-Ming Tu,
DMEPA TL
DRISK: Naomi Redd, Risk
Management
Reviewer

OPDP

Nicholas Senior

Labeling

Jennie Chang, Associate
Director

OSI Inspections

Susan Thompson, OSI TL
Lauren Iacono-Connor, OSI
Reviewer

Agenda Items:

1. Updates

- a. Dr. Keegan informed the review team of an early action date, scheduled for March 23, 2017.
- b. All primary reviews to be completed by February 23, 2017. As the multidisciplinary review document will capture detailed discipline reviews, reviewers are only expected to upload a memorandum stating their recommendation for or against approval action, and reference the multidisciplinary review, by the February 23, 2017 date.
- c. All PMR/PMC language should be sent to CDTL no later than COB Tuesday, February 14, 2017 for review. Final PMR-PMC will be forwarded to the Safety Director by February 17, 2017.

The following PMC/PMRs were identified and discussed:

- Nonclinical—pending
- Clinical—pending
- Clinical Pharmacology

Conduct an assessment of treatment-emergent binding and neutralizing anti-drug antibody (ADA) responses with validated assays (the neutralizing assay as requested in PMC X) 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 ADA response 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.

- CMC (+1 pending, dependent on Sponsor response to IR)

(b) (5)

2. MISCELLANEOUS ITEMS/ISSUES

- SGE clearance process initiated. Identified David Kelsen and Kristin Burr (patient representative)
- PMR/PMC Discussion

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/s/

IDARA UDOH
04/05/2017

Udoh, Idara

From: Udoh, Idara
Sent: Thursday, March 23, 2017 9:54 AM
To: 'Virginia Pappalardo'
Subject: RE: [Courtesy Copy: FDA Proposed Edits to PI/Proposed PMC Language] BLA 761049/EMD Serono/Treatment of Merkel Cell Carcinoma

Thank you, Virginia, for your 3/21 submission of the package insert (PI) and your 3/22 submission of the Medication Guide.

As discussed during our call earlier today, please revise the Highlights and Section 1 of the PI, and any other section of the PI where the indication statement references

“treatment of adult and pediatric patients 12 years and older”

and change it to

“treatment of adults and pediatric patients 12 years and older”

The same change should be made with the Medication Guide if “adult” is in the singular form. Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

From: Virginia Pappalardo [mailto:virginia.pappalardo@emdserono.com]
Sent: Tuesday, March 21, 2017 11:53 AM
To: Udoh, Idara
Subject: RE: [Courtesy Copy: FDA Proposed Edits to PI/Proposed PMC Language] BLA 761049/EMD Serono/Treatment of Merkel Cell Carcinoma
Importance: High

Dear Idara,
Please find attached the revised PI (both clean and tracked change versions in both WORD and PDF formats), as well as the clinical information amendment confirming our agreement with the pediatric PMC. We also included a brief overview of the planned pediatric study, along with the milestone dates. Could you please confirm receipt of this email at your earliest convenience? The official amendment through the EST will follow later today. Thanks!

Kindest regards,
Virginia

Virginia Pappalardo, RAC

Associate Director, Global Regulatory Lead, Immuno-Oncology
EMD Serono Research and Development Institute, Inc. | Global Regulatory Affairs & Quality Assurance



A business of Merck KGaA, Darmstadt, Germany

EMD Serono R&D | 45A Middlesex Turnpike | Billerica, MA 01821 | USA
Phone: 1-978-294-1617 | Mobile: (b) (6) | Fax: 1-978-215-4044
E-mail: virginia.pappalardo@emdserono.com

Upcoming out of office: March 22-24 (vacation), March 27-31 (offsite meeting)

From: Udoh, Idara [<mailto:Idara.Udoh@fda.hhs.gov>]
Sent: Tuesday, March 21, 2017 8:47 AM
To: Virginia Pappalardo <virginia.pappalardo@emdserono.com>
Subject: [Courtesy Copy: FDA Proposed Edits to PI/Proposed PMC Language] BLA 761049/EMD Serono/Treatment of Merkel Cell Carcinoma

Good morning, Virginia. I hope this message finds you well.

Please find attached FDA's preliminary edits and comments (in clean and tracked versions) to your revised package insert (PI) labeling submitted on March 16, 2017. In addition, there is proposed PMC language for a new pharmacovigilance study.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From EMD Serono" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From EMD Serono" in the comment field) and include justification for your counterproposal.

A response to FDA's proposed changes and the proposed PMC with milestone completion dates is requested by **2:00 PM, EST today March 21, 2017**. In addition to submitting your response to the BLA, please email me a copy of your responses as well as a clean and redlined version of the labeling.

Please acknowledge receipt.

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
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/s/

IDARA UDOH
03/23/2017

Udoh, Idara

From: Virginia Pappalardo <virginia.pappalardo@emdserono.com>
Sent: Wednesday, March 22, 2017 12:05 PM
To: Udoh, Idara
Subject: RE: Question - medication guide
Attachments: Avelumab Medication Guide MCC 2017-03-22 clean sub.pdf; Avelumab Medication Guide MCC 2017-03-22 TC sub.docx; Avelumab Medication Guide MCC 2017-03-22 TC sub.pdf; Avelumab Medication Guide MCC 2017-03-22 clean sub.docx

Dear Idara

Please find attached the revised medication guide. Could you please advise whether we should formally submit this through the ESG as well? Thanks in advance.

Kindest regards,
Virginia

From: Virginia Pappalardo
Sent: Wednesday, March 22, 2017 11:52 AM
To: Udoh, Idara <Idara.Udoh@fda.hhs.gov>
Subject: Re: Question - medication guide

Yes we accept. Should we still plan to submit a revision or is this email sufficient?

Virginia

On Mar 22, 2017, at 11:51 AM, Udoh, Idara <Idara.Udoh@fda.hhs.gov> wrote:

Does EMD Serono accept our proposed language?

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

From: Virginia Pappalardo [<mailto:virginia.pappalardo@emdserono.com>]
Sent: Wednesday, March 22, 2017 11:47 AM
To: Udoh, Idara
Subject: Re: Question - medication guide

I will get this to you is email within the next half hour latest and we will follow up with the formal submission through ESG later today.

Thanks!
Virginia

On Mar 22, 2017, at 11:41 AM, Udoh, Idara <Idara.Udoh@fda.hhs.gov> wrote:

Virginia, we propose the following:

"It is not known if Bavencio is safe and effective in children under the age of 12 ."

If you accept, please send the final Medication Guide as soon as possible.

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

From: Virginia Pappalardo [<mailto:virginia.pappalardo@emdserono.com>]
Sent: Wednesday, March 22, 2017 11:29 AM
To: Udoh, Idara
Subject: Re: Question - medication guide

Hi Idara

Here is a proposal for revising: It is not known if BAVENCIO is safe and effective in children **below 12 years**.

Please let us know if you have an alternative or whether the medication guide, as is, is sufficient.

Virginia

On Mar 22, 2017, at 11:00 AM, Virginia Pappalardo
<virginia.pappalardo@emdserono.com> wrote:

Dear Idara

The current medication guide includes the following:

"It is not known if Bavencio is safe and effective in children." As our indication now includes pediatric patients 12 and older, should we revise the medication guide immediately?

Virginia

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/s/

IDARA UDOH
03/22/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 21, 2017
From: Idara Udoh, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049/ Type 1 NME/ BAVENCIO (avelumab)/ EMD Serono, Inc.
Package Insert and Proposed PMC Language

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

Dear Ms. Pappalardo:

Please find attached additional FDA edits and comments to your package insert (PI) labeling submitted on March 16, 2017, which was in response to our March 14, 2017 information request. We also refer to our March 14, 2017 proposed PMR/PMC language, and acknowledge your March 16, 2017 response.

In areas of the PI that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From EMD Serono" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From EMD Serono" in the comment field) and include justification for your counterproposal.

APPEARS THIS WAY ON ORIGINAL

Additionally, in order to support the expanded indication in the PI, since there is virtually no safety data in the pediatric population, we will require the following Post Marketing Commitment (PMC):

CLINICAL

Conduct an Enhanced Pharmacovigilance Study in a sufficient number of pediatric patients age(s) 12-18 to adequately characterize baseline risk factors and safety outcomes following exposure to avelumab. The study, at a minimum, will include the following key elements:

- Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
- Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern.
- Data collected prospectively analyzed separate from data collected retrospectively.

There will be interim annual reporting of the data collected from the study.

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>MM/DD/YYYY</u>
Other: _____	<u>MM/DD/YYYY</u>

Please provide a response to FDA's proposed edits, in addition to your agreement and milestones for the proposed PMC, by 2:00 PM, EST on March 21, 2017. In addition to submitting your response to the BLA, please provide a courtesy copy, via email, of your responses as well as a clean and redlined (track changes) version of the PI labeling.

Ensure that you review the PI carefully before submitting the final, agreed-upon PI. Please let me know if you have any questions.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

Attachment: FDA Proposed Edits to Package Insert (as of 3.21.2017)

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/s/

IDARA UDOH
03/21/2017

Udoh, Idara

From: Udoh, Idara
Sent: Monday, March 06, 2017 4:28 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review; to our March 3, 2017 proposed edits to your package insert (PI) labeling and Medication Guide; and your March 6, 2017 response to the proposed edits. We also refer to our March 6, 2017 teleconference to discuss your response.

Upon further review, the following lines of the PI require additional edits. Lines 296-297 describing serious adverse events should read as follows:

Serious adverse reactions that occurred in more than one patient were acute kidney injury, anemia, abdominal pain, ileus, asthenia and cellulitis.

Please update the draft PI that you intend to re-submit, per our March 6th discussion, to include the above language. Submit your response formally to BLA761049, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
03/14/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 14, 2017
From: Idara Udoh, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049/ Type 1 NME/ BAVENCIO (avelumab)/ EMD Serono, Inc.

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

Dear Ms. Pappalardo:

Please find attached additional FDA edits and comments to your package insert (PI) labeling submitted on March 7, 2017, which was in response to our March 6, 2017 information request.

In addition to these proposed edits, please ensure all tables and figure numbers are updated (if needed), and formatting corrected, as needed. Regarding your PI, you are responsible for submitting prescribing information that meets the Selected Requirements of Prescribing Information (SRPI) requirements. Please refer to the SRPI checklist on the *PLR Requirements for Prescribing Information* website found at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From EMD Serono" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From EMD Serono" in the comment field) and include justification for your counterproposal.

Please provide a response to FDA's proposed edits no later than 1:00 PM, EST on March 16, 2017. In addition to submitting your response to the BLA, please provide a courtesy copy, via email, of your responses as well as a clean and redlined (track changes) version of the PI labeling.

Please note these are our preliminary comments and additional comments may follow.

Please let me know if you have any questions.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

Attachment: FDA Proposed Edits to Package Insert (as of 3.14.2017)

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IDARA UDOH
03/14/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 3, 2017
From: Idara Udoh, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049/ Type 1 NME/ BAVENCIO (avelumab)/ EMD Serono, Inc.

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

Dear Ms. Pappalardo:

Please find attached additional FDA edits and comments to your package insert (PI) labeling submitted on February 17, 2017 and February 20, 2017, which was in response to our February 10, 2017 information request. Additionally, we are providing preliminary edits and comments to your Medication Guide that was submitted on September 23, 2016.

In addition to these proposed edits, please update all tables and figure numbers (if needed), and correct formatting, as needed. Regarding your PI, you are responsible for submitting prescribing information that meets the Selected Requirements of Prescribing Information (SRPI) requirements. Please refer to the SRPI checklist on the *PLR Requirements for Prescribing Information* website found at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From EMD Serono" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From EMD Serono" in the comment field) and include justification for your counterproposal.

Please provide a response to FDA's proposed edits by 12:00 PM, EST on March 6, 2017. In addition to submitting your response to the BLA, please provide a courtesy copy, via email, of your responses as well as a clean and redlined (track changes) version of the PI labeling.

Please note these are our preliminary comments and additional comments may follow.

Please let me know if you have any questions.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

Attachment: FDA Proposed Edits to Package Insert (as of 3.3.2017) and Medication Guide

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/s/

IDARA UDOH
03/14/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 14, 2017
From: Idara Udoh, M.S., Senior Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049, Bavencio (avelumab), EMD Serono, Inc.: Proposed PMC/PMR Language

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) submitted under section 351(a) of the Public Health Service Act for Bavencio (avelumab) Injection, for intravenous use, 20 mg/mL.

Please note that additional post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposals. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter; therefore, the exact language of the proposed PMRs/PMCs below may change, although the intent will remain the same. We are requesting that you respond to our proposal by **close of business on March 15, 2017.**

PMRs Subject to the Reporting Requirements Under Section 505(o)

CLINICAL

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:
Final Report Submission:

6/30/2021

12/30/2021

Please let me know if you have any questions or concerns.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

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/s/

IDARA UDOH
03/14/2017

Udoh, Idara

From: Udoh, Idara
Sent: Friday, February 24, 2017 3:16 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review. Our clinical reviewer has the following comment, and requests a response no later than noon **February 28, 2017**:

Please send the hematology and laboratory datasets for Study 003 (do not include pooled data) to support Table 3 in the proposed package insert which presents on-treatment worsening of specific laboratory abnormalities based on the 90 day safety update. Provide detailed instructions on what flags/columns were used to obtain the results in this table.

Please submit your response formally to BLA761049, by the date specified above, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

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IDARA UDOH
03/01/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 23, 2017
From: Idara Udoh, M.S., Senior. Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049/ Type 1 NME/ BAVENCIO (avelumab)/ EMD Serono, Inc.

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

Dear Ms. Pappalardo:

FDA refers to the February 2, 2017, preliminary comments regarding your proposed carton and container labeling submitted on September 23, 2016; and we acknowledge your response received February 10, 2017.

Please find an additional comment regarding the carton labeling, and provide a response by close of business March 2, 2017. In addition to formally submitting your response to the BLA, please email me a copy of your response to our comment, as well as the revised carton and container labeling.

A. Carton Labeling

1. Revise the statement on the side panel “(b) (4)” to comply with [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex Guidance for Industry and Food and Drug Administration Staff, March 2013](#). Additionally, “(b) (4)” is a regulatory term that is not commonly used in labeling. Consider the language you agreed to in the PI. For example: “The vial stopper is not made with natural rubber latex.”

Please let me know if you have any questions or concerns.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

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IDARA UDOH
02/23/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 17, 2017
From: Idara Udoh, M.S., Senior Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049, Bavencio (avelumab), EMD Serono, Inc.: Proposed PMC/PMR Language

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) submitted under section 351(a) of the Public Health Service Act for Bavencio (avelumab) Injection, for intravenous use, 20 mg/mL.

Please note that additional post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposals. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter; therefore, the exact language of the proposed PMRs/PMCs below may change, although the intent will remain the same. We are requesting that you respond to our proposal by **close of business on Monday, February 20, 2017.**

PMRs Subject to the Reporting Requirements Under Section 505(o)

CLINICAL

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 to be followed for a minimum of 12 months to establish the objective response rate and characterize the durability of response. Overall survival will be followed to maturity until at least 70% of patients have died, or for an additional two years beyond the primary data analysis cut-off, to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided

Final Protocol Submission:
Study/Trial Completion:

MM/DD/YYYY
MM/DD/YYYY

Final Report Submission:	<u>MM/DD/YYYY</u>
Other: _____	<u>MM/DD/YYYY</u>

PMCs Subject to the Reporting Requirements Under Section 505(o)

CLINICAL PHARMACOLOGY

2. 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 assay and the neutralizing assay as requested in PMC 1) 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 ADA response should 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 cut-point.

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>MM/DD/YYYY</u>
Other: _____	<u>MM/DD/YYYY</u>

PRODUCT QUALITY

3. 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.

Final Report Submission:	<u>MM/DD/YYYY</u>

PRODUCT QUALITY MICROBIOLOGY

4. 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.

Final Report Submission:	<u>3/23/2018</u>

NONCLINICAL

5. 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 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 an evaluation of cytokine production by T cells at appropriate time-points.

Final Protocol Submission:	<u>MM/DD/YYYY</u>
Study/Trial Completion:	<u>MM/DD/YYYY</u>
Final Report Submission:	<u>MM/DD/YYYY</u>
Other: _____	<u>MM/DD/YYYY</u>

Please let me know if you have any questions or concerns.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

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/s/

IDARA UDOH
02/17/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/14/2017 11:22:28 AM

To: virginia.pappalardo@emdserono.com

CC: Idara.Udoh@fda.hhs.gov; truong.quach@fda.hhs.gov

BCC:

Subject: CUMULATIVE INFORMATION REQUEST BLA 761049

Dear Virginia,

We have cumulative IR that we would like to request by 15 February 2017 if possible.
Please confirm that you have received this communication.

Best Regard.

Truong Quach, Pharm.D.

Regulatory Business Process Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **15 February 2017**.

We have the following information request:

FDA comments on the response submitted in amendment dated February 06, 2017:

The summary provided in your February 6, 2016 IR response is insufficient to evaluate the adequacy of the transfer to the Merck Serono S.A site as DP QC release testing site. Provide the cited method transfer report numbers for evaluation.

FDA comments on the response submitted in amendment dated February 13, 2017:

(b) (4)



If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

Truong
Quach
-S

Digitally signed by
Truong Quach -S
DN: cn=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Truong Quach -S,
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Date: 2017.02.14
11:10:17 -05'00'

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 10, 2017
From: Idara Udoh, M.S., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049/ Type 1 NME/ BAVENCIO (avelumab)/ EMD Serono, Inc.

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

Dear Ms. Pappalardo:

Please find attached FDA's preliminary edits and comments to your package insert (PI) labeling submitted on December 23, 2016, which was based on 12-month efficacy update and a 90-day safety report omitted from your revised December 13, 2016 PI labeling.

In addition to these proposed edits, please update the Table of Contents and tables and figure numbers (if needed), and correct formatting, as needed. You are responsible for submitting prescribing information that meets the Selected Requirements of Prescribing Information (SRPI) requirements. Please refer to the SRPI checklist on the *PLR Requirements for Prescribing Information* website found at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

In areas of the label that you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From EMD Serono" in the comment field) stating your agreement.

For those edits which you do not agree, provide a comment (cite "From EMD Serono" in the comment field) and include justification for your counterproposal.

Please provide a response to FDA's proposed edits by 12:00 PM, EST on February 17, 2017. In addition to submitting your response to the BLA, please provide a courtesy copy, via email, of your responses as well as a clean and redlined (track changes) version of the PI labeling. We will contact you shortly to schedule a teleconference to be held during the week of February 20, 2017 to begin discussions on your forthcoming responses and revised labeling.

Please note these are our preliminary comments, and this labeling is currently being reviewed by our counterparts in the Office of Prescription Drug Promotion (OPDP) and the Patient Labeling Team (PLT) and additional comments may follow.

Please let me know if you have any questions.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

Attachment: FDA Proposed Edits to Package Insert (as of 2.10.2017)

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/s/

IDARA UDOH
02/10/2017

Udoh, Idara

From: Udoh, Idara
Sent: Thursday, February 09, 2017 11:26 AM
To: 'Virginia Pappalardo'
Subject: RE: reminder regarding FDA definition for resolution of immune-mediated endocrinopathies [FDA Clinical Information Request/BLA761049]

Thank you for your patience, Virginia, while FDA gathered the definition for EMD Serono.

In addition to the definition (below), our clinical reviewer is requesting that you analyze your data using this definition. Please provide a response by COB, February 15, 2017:

Patients who experience an immune-mediated adverse reaction during treatment with avelumab should not be considered to have an adverse event outcome of “resolved” unless the patient is asymptomatic and not requiring continued treatment for the reaction (i.e., corticosteroids, hormone replacement therapy, any medical management). Provide an analysis of the safety data for Study 003 (n=88) and the pooled population from Study 001 and 003 (N=1738) that defines resolution as clinically asymptomatic and off all concomitant medications that were initiated in response to the immune-mediated adverse reaction. State the proportion of patients with any immune-mediated adverse reaction that had resolution and the proportion of patients within specific categories of immune adverse reactions (e.g., adrenal insufficiency, thyroid disorders, diabetes etc.) that experienced resolution using this definition. Additionally, provide the resolution rates by severity of the reaction (i.e., all grade events and $\geq$ Grade 3 events).

Your response to this request should be formally submitted to BLA761049 by the date specified above, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

From: Virginia Pappalardo [<mailto:virginia.pappalardo@emdserono.com>]
Sent: Wednesday, February 08, 2017 5:41 PM
To: Udoh, Idara
Subject: reminder regarding FDA definition for resolution of immune-mediated endocrinopathies

Hi Idara

Quickly following up from our call yesterday where I requested the FDA definition for resolution of immune-mediated endocrinopathies. As a reminder, during the January 31st teleconference we committed to providing updated analyses on the resolution rate of endocrinopathies, pending receipt of the definition from FDA. By any chance is your clinical team able to provide this definition? Thank you in advance.

Kindest regards,
Virginia

Virginia Pappalardo, RAC

Associate Director, Global Regulatory Lead, Immuno-Oncology
EMD Serono Research and Development Institute, Inc. | Global Regulatory Affairs & Quality Assurance



A business of Merck KGaA, Darmstadt, Germany

EMD Serono R&D | 45A Middlesex Turnpike | Billerica, MA 01821 | USA
Phone: 1-978-294-1617 | Mobile: (b) (6) | Fax: 1-978-215-4044
E-mail: virginia.pappalardo@emdserono.com

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/s/

IDARA UDOH
02/09/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/07/2017 04:28:55 PM

To: virginia.pappalardo@emdserono.com

CC: Idara.Udoh@fda.hhs.gov; truong.quach@fda.hhs.gov

BCC:

Subject: INFORMATION REQUEST BLA 761049

Dear Virginia,

I have another IR request for BLA 761049 and would like a response by February 13, 2017.
Please confirm that you have received this email communication.

Thank you,

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **13 February 2017**.

We have the following information request:

Process Validation

Media fill

1. Media fill Batch number 688G007 filled in 25 May 2016 supports the maximum sterile hold duration of (b) (4) and the maximum filling time (b) (4) for the avelumab DP. You have agreed to conduct media fills once per year, combining both the maximum sterile hold time (b) (4) and maximum filling time (b) (4) in the same batch starting from 2017. Confirm the implementation of this strategy and submit the information and summary data from the first 2017 media fill as a post marketing commitment.

(b) (4)

(b) (4)

Validation of Analytical procedures

1. Clarify if sterility and endotoxin testing of the avelumab drug product is performed at Merck Serono S.p.A., Guidonia Montecelio (Roma), Italy site and submit the method qualification/verification data to support the performance of these tests at this site.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

Truong
Quach
-S

Digitally signed by
Truong Quach -S
DN: c=US, o=U.S.
Government,
ou=HHS, ou=FDA,
ou=People,
cn=Truong Quach -S,
0.9.2342.19200300.1
00.1.1=2001511949
Date: 2017.02.07
16:09:02 -05'00'

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Udoh, Idara

From: Udoh, Idara
Sent: Monday, February 06, 2017 8:30 AM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good morning, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review. Our clinical reviewer has the following comment, and requests a response no later than **COB February 13, 2017**:

Provide a summary table of common laboratory abnormalities occurring in patients enrolled in Study 003 and in the pooled population during treatment with avelumab. Include columns for any grade abnormality and $\geq$ Grade 3 abnormalities. The following format (or something similar) would be acceptable.

Preferred Term	Study 003 N=88 n (%)		Pooled analysis N=1738 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Chemistry				
Increased creatinine				
Increased lipase				
Increased amylase				
Hyperglycemia				
Increased serum creatine kinase				
Increased bilirubin				
Increased alanine aminotransferase				
Increased alkaline phosphatase				
Increased aspartate aminotransferase				
Hypokalemia				
Hypocalcemia				
Hypercalcemia				
Hypomagnesemia				
Hypophosphatemia				
Hematology				
Anemia				

Preferred Term	Study 003 N=88 n (%)		Pooled analysis N=1738 n (%)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Lymphopenia				
Neutropenia				
Thrombocytopenia				

Please submit your response formally to BLA761049, by the date specified above, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
02/06/2017

Udoh, Idara

From: Udoh, Idara
Sent: Wednesday, February 01, 2017 12:42 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia.

In response to your recent 1/31/2017 submission, FDA acknowledges EMD Serono's sensitivity analysis. However, FDA is requesting an analysis of treatment emergent adverse events that led to temporary discontinuation of avelumab in Study 003 and the pooled safety population (n=1738) with exclusion of only those patients who had a temporary interruption of avelumab for an infusion reaction but restarted avelumab the same day. Include patients (if any) with infusion reactions that led to temporary discontinuation but for whom avelumab was not restarted the same day.

Please submit your response formally to BLA761049, by COB February 3, 2017, in addition to providing a courtesy copy to me via email.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

From: Virginia Pappalardo [mailto:virginia.pappalardo@emdserono.com]
Sent: Tuesday, January 31, 2017 11:52 AM
To: Udoh, Idara
Subject: RE: FDA Information Request (Clinical Pharmacology): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Dear Idara

Today we've submitted responses to the January 24th Clinical IR and the January 27th Clinical Pharmacology IR. The responses were sent in the same amendment, however, we've separated the response documents to make it easier for you to forward to the appropriate review teams.

As such, please find attached the clinical response document and two appendices that accompany that response (PDFs titled information-amendments-other_31Jan2017, clinical-ir-appendix-1 and clinical-ir-appendix-2). If you would like the appendices in excel format, I am able to provide. Please let me know. Additionally please find attached the clinical pharmacology response (PDF titled immunogenicity-information-request_31Jan2017).

Could you please confirm receipt of this message and attachments, as well as the formal submission through the gateway? Thanks in advance.

Kindest regards,
Virginia

Virginia Pappalardo, RAC
Associate Director, Global Regulatory Lead, Immuno-Oncology

EMD Serono R&D | 45A Middlesex Turnpike | Billerica, MA 01821 | USA
Phone: 1-978-294-1617 | Mobile: (b) (6) | Fax: 1-978-215-4044
E-mail: virginia.pappalardo@emdserono.com

From: Udoh, Idara [<mailto:Idara.Udoh@fda.hhs.gov>]
Sent: Friday, January 27, 2017 2:45 PM
To: Virginia Pappalardo <virginia.pappalardo@emdserono.com>
Subject: FDA Information Request (Clinical Pharmacology): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review. Our clinical pharmacology reviewer has the following comment, and requests a response no later than COB **February 1, 2017**:

Reference is made to section 3.3.1 of the 90-Day Safety Update Report: Provide clarification regarding the population of patients included in the 1558 patients treated with avelumab who underwent immunogenicity testing. What range of doses was administered across this group, and what number of patients in each dose cohort tested positive for treatment-emergent anti-drug antibodies (ADA)? Additionally, provide the reason(s) why some patients treated with avelumab were not evaluable for immunogenicity.

Please submit your response formally to BLA761049, by the date specified above, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
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/s/

IDARA UDOH
02/02/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 1, 2017
From: Idara Udoh, M.S., Senior. Regulatory Health Project Manager DOP2/OHOP
Subject: BLA 761049/ Type 1 NME/ BAVENCIO (avelumab)/ EMD Serono, Inc.

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

Dear Ms. Pappalardo:

Please find attached FDA's preliminary comments regarding your proposed carton and container labeling submitted on September 23, 2016.

Provide a response to FDA's proposed changes by close of business February 10, 2017. In addition to formally submitting your response to the BLA, please email me a copy of your responses to our comments below, as well as the revised carton and container labeling.

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.
2. Indicate how the label is affixed to the vial and where the visual area of inspection is located, per 21 CFR 610.60(e).

B. Container Label and Carton Labeling

1. Increase the prominence of the dosage form "Injection" by matching the font size of the proper name.
2. Revise the dosage form "injection" to read "Injection" per USP General Chapters: <1> Injections, Nomenclature and Definitions.
3. Consider revising the NDC numbers of the container label and carton labeling. The container label and carton labeling can be assigned the same NDC since the product is supplied as a single vial within a single carton.

C. Container Label

1. We find the container label is a partial label per 21 CFR 610.60(c). Therefore, we recommend the following interventions to make space on the recommendation below:
 - a. Delete the statement, “(b) (4)” This statement is not required on a partial label.
 - b. Delete (b) (4). This statement is not required on a partial label.
2. As currently presented, the NDC number is located on the side panel of the container label. Since NDC numbers are often used as additional verification prior to drug dispensing in the pharmacy, when presented, it should be prominently displayed in the top third of the principal display panel (PDP) of the labeling in accordance with 21 CFR 207.35(b)(3)(i).
3. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the container label whenever possible. Therefore, we request you add the product barcode to the container label as required per 21CFR 201.25(c)(2). Consider orienting the barcode in a vertical position to make the barcode easier to scan using a barcode scanner.
4. The container label appears crowded. Important product information should be displayed with prominence on the PDP. This may be achieved by creating a side panel and relocating other information to the side panel. Example layout below demonstrates our recommendation only (not to size, spacing, color, etc.). Of note, we recommend mix case letters “For Intravenous Use Only” instead of all upper case to improve readability. Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.

PDP	Side Panel
NDC 44087-3535-2 Bavencio (avelumab) Injection 200 mg/ 10 mL (20 mg/ mL) For intravenous infusion after dilution Single-dose vial. Discard unused portion.	Rx only Storage and handling information. Warning statement Manufacturer information Lot Exp 

D. Carton Labeling

1. Revise the statement “(b) (4)” which appears on the side panel to read “Usual Dose: See prescribing information.”

2. It appears that “^{(b) (4)}” is your attempt to fulfill the country of origin requirement per 19 CFR 134.11. If so, we recommend revising the statement to “Product of Switzerland”. We are aiming to provide consistency with labeling the country of origin.

Please let me know if you have any questions or concerns.

Sincerely,

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-3074

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/s/

IDARA UDOH
02/01/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 02/01/2017 09:01:59 AM
To: virginia.pappalardo@emdserono.com
CC: Idara.Udoh@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST BLA 761049

Dear Virginia,

We are requesting another round of IR and we would like a response by Feb. 6, 2017.
Please confirm that you have received this email communication.

Thank you.

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research,



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We also refer to your amendment dated 09 December 2016 submission, containing your response to our CMC information request.

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **06 February 2017**.

We have the following information request:

1. You stated in your response dated on 12/9/2016 that all analytical methods were initially developed and validated at Merck Serono Guidonina Montecelio, Italy and no data were submitted for method transfer process to qualify the Merck Serono S.A, Switzerland site as the DP lot release testing site. Confirm your intent to (b) (4)

2. We acknowledge that your process characterization studies showed a limited impact on CQAs over the (b) (4)

We recommend you revise your proposed ranges based on this additional characterization data or provide additional justification.

3.

(b) (4)

4. Recent information suggests that nanoparticles can be shed from a filling pump's solution-contact surfaces which may then nucleate protein aggregation and/or particulate formation. It is recommended that in addition to USP <788> particulate testing, sub-visible particles <10 micron in size also be characterized. Provide any additional data available describing the evaluation of particles of these size in avelumab DP.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

Truong
Quach -
S

Digitally signed by Truong
Quach -S
DN: cn=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
c=Truong Quach -S,
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Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



BLA761049

MID-CYCLE COMMUNICATION

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 Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Bavencio (avelumab) Injection, for intravenous use, 20 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on January 5, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MID-CYCLE COMMUNICATION

Meeting Date and Time: January 5, 2017; 2:00 PM – 3:00 PM

Application Number: BLA761049
Product Name: Bavencio (avelumab)
Indication: Treatment of patients with metastatic Merkel cell carcinoma
Applicant Name: EMD Serono, Inc.

Meeting Chair: Suzanne Demko
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Richard Pazdur, Director, Office of Hematology and Oncology Products (OHOP)
Amy McKee, Acting Deputy Office Director, OHOP
Patricia Keegan, Director, Division of Oncology Products (DOP2), OHOP
Suzanne Demko, Clinical Team Leader, DOP2/ OHOP
Denise Casey, Clinical Reviewer, DOP 2/ OHOP
Idara Udoh, Senior Regulatory Project Manager, DOP2/ OHOP
Anuja Patel, Senior Regulatory Project Manager, DOP2/ OHOP
Whitney Helms, Nonclinical Team Leader, Division of Hematology/Oncology Toxicology Products, OHOP
Joel Welch, Product Quality Team Leader, Office of Biotechnology Products (OBP)
Arulvalthani Arudchandran, Product Quality Reviewer, OBP
Lakshmi Narasimhan, Microbiology Reviewer, OBP
Nan Zheng, Pharmacometrics Reviewer, Office of Clinical Pharmacology
Pallavi Mishra-Kalyani, Biometrics Team Reviewer, Office of Translational Sciences
Shaily Arora, Safety Evaluator, Office of Surveillance and Epidemiology (OSE)
Carolyn McCloskey, Epidemiologist, OSE

EMD SERONO, INC. ATTENDEES

Virginia Pappalardo, Global Regulatory Lead, Global Regulatory Affairs, EMD Serono
Jennifer Stevens, Global Regulatory Affairs Program Lead, EMD Serono
Philippe Serrano, Global Head, Regulatory Affairs Oncology, Merck KGaA
Jacques Mascaro, Senior Vice President, Head of Global Regulatory Affairs and R&D Quality, Merck KGaA
Achta Paraiso, Manager, Biotech Regulatory CMC Unit, Merck KGaA
Kevin Chin, Executive Medical Director, Immuno-Oncology, Global Research & Early Development, EMD Serono
Meliessa Hennessy, Global Clinical Development
Anja von Heydebreck, Global Statistics, Merck KGaA

Berend Neuteboom, Senior Global Early Development Lead, EMD Serono
Haiqing (Isaac) Dai, Director, Clinical Pharmacology, EMD Serono
Laurie Strawn, Global Regulatory, Pfizer
Cecile Lloret
Gülseren Güzel, Global Drug Safety, Merck KGaA

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES

No significant review issues have been identified to date.

INFORMATION REQUESTS

Clinical:

Are there clinical data to support an indication for avelumab that includes patients with newly diagnosed metastatic Merkel cell carcinoma in addition to patients who have progressed following prior chemotherapy? If so, submit a summary of these data, or indicate where in the application the data can be located.

Discussion During Meeting: EMD Serono stated that there are no clinical data in the application for the first-line cohort, but the sample size intended in the first-line is 112 patients. Durable response is the primary endpoint with a 6-month duration of response. FDA advised that if EMD Serono is interested in a broader indication, they should make an argument for why FDA should grant a broader indication for something not demonstrated, and why it is imperative that an expanded indication for the first-line treatment of MCC be granted. Any data or information on the use of chemotherapy after the drug would also be helpful, considering lack of confidence in subsequent responses to multiple therapies for first-line patients. EMD Serono agreed to submit the information to the BLA, within one week.

CMC:

An information request issued on January 4, 2017, with a response due on January 10, 2017.

MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time. Also, there is no need for a REMS associated with this application.

ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee meeting.

POST MARKETING REQUIREMENT/COMMITMENT (PMR/PMC)

CMC:

PMC

- 1) 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.

2)



Discussion During Meeting: EMD Serono agreed to submit its available validation data in addition to its response to the CMC information request, due January 10, 2017.

LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

Proposed labeling and any PMR/PMC requests are due to be sent to EMD Serono by February 23, 2017.

The Late-Cycle Meeting between you and the review team is currently scheduled for March 23, 2017. We intend to send the briefing package to you approximately 10-12 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review.

Discussion During Meeting: FDA explained that the completed and reviewed label, containing FDA comments, will be sent to EMD Serono by February 23, 2017. There is a 1-2 week turnaround for the label from EMD Serono prior to expected return of the label to FDA and labeling negotiations beginning.

FDA acknowledged and agreed to EMD Serono's request for a teleconference format for its Late-Cycle Meeting.

EMD Serono inquired about submission of the Pre-Launch Activities Importation Request. FDA advised EMD Serono to submit within 60-days of their BLA PDUFA goal (i.e. mid-to-late March 2017).

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/s/

IDARA UDOH
01/30/2017

Udoh, Idara

From: Udoh, Idara
Sent: Friday, January 27, 2017 2:45 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical Pharmacology): BLA761049/EMD
Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review. Our clinical pharmacology reviewer has the following comment, and requests a response no later than COB **February 1, 2017**:

Reference is made to section 3.3.1 of the 90-Day Safety Update Report: Provide clarification regarding the population of patients included in the 1558 patients treated with avelumab who underwent immunogenicity testing. What range of doses was administered across this group, and what number of patients in each dose cohort tested positive for treatment-emergent anti-drug antibodies (ADA)? Additionally, provide the reason(s) why some patients treated with avelumab were not evaluable for immunogenicity.

Please submit your response formally to BLA761049, by the date specified above, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
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301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
01/30/2017

Udoh, Idara

From: Udoh, Idara
Sent: Monday, January 30, 2017 3:14 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review.

Our clinical reviewer requests that you submit the case report form for patient 100070-001-403-0013. Also, please verify whether the adverse reactions of chills and pyrexia this patient experienced on Study Day 1 was considered an infusion-related reaction and captured in the adverse event incidence rates as such.

Your response to this request should be formally submitted to BLA761049 **no later than COB February 3, 2017**, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
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idara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
01/30/2017

Udoh, Idara

From: Udoh, Idara
Sent: Thursday, January 26, 2017 11:51 AM
To: 'Virginia Pappalardo'
Subject: RE: Clinical Information Request: BLA 761049/ EMD Serono/ Bavencio (avelumab)

Virginia:

In reference to your response to our January 18, 2017 clinical information request, received yesterday January 25, 2017, please provide a copy of Appendix 1 to me via email, as soon as possible, in Excel format. Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
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301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

From: Virginia Pappalardo [<mailto:virginia.pappalardo@emdserono.com>]
Sent: Wednesday, January 25, 2017 1:13 PM
To: Udoh, Idara
Subject: RE: Clinical Information Request: BLA 761049/ EMD Serono/ Bavencio (avelumab)

Dear Idara,
Today we submitted a response to the clinical IR sent by Anuja last week. A courtesy copy of the response document and Appendix are attached (note, the formal amendment contains CRFs that I have not attached to this email). Please confirm receipt of this message. Thanks!

Kindest regards,
Virginia

Virginia Pappalardo, RAC
Associate Director, Global Regulatory Lead, Immuno-Oncology

EMD Serono R&D | 45A Middlesex Turnpike | Billerica, MA 01821 | USA
Phone: 1-978-294-1617 | Mobile: (b) (6) | Fax: 1-978-215-4044
E-mail: virginia.pappalardo@emdserono.com

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Wednesday, January 18, 2017 7:27 AM
To: Virginia Pappalardo <virginia.pappalardo@emdserono.com>
Cc: Udoh, Idara <Idara.Udoh@fda.hhs.gov>

Subject: Clinical Information Request: BLA 761049/ EMD Serono/ Bavencio (avelumab)

Importance: High

Hello Virginia,

I am writing to you on behalf of your Regulatory Contact, Idara Udoh who is currently out of the office.

We refer to your BLA application for avelumab which is currently under our review.

Our clinical team has the following request for additional information and requests a response to be formally submitted to the BLA no later than January 25, 2017. Please email me (CC: Idara Udoh) a courtesy copy of the response.

- 1. Please provide information on all patients from Study 003 who were treated beyond radiologic progression. State the subject ID, the reason for continuing treatment, and the outcomes (e.g., a subsequent response, progressive disease, eventual discontinuation). Provide relevant dates and durations of any response that developed after progression. A table format would be acceptable. Also submit the case report forms for these patients.**
- 2. Provide a summary table of all patients who received corticosteroids during Study 003. Include the subject ID, the adverse event (or other reason) leading to steroid administration, whether the AE was considered related to avelumab, the specific steroid medication administered, the formulation, whether it was “high-dose” steroid therapy or not, duration of treatment, action taken with regard to study drug (continued, interrupted or discontinued), the AE outcome and whether there was recurrence if the patient continued to receive avelumab after the event.**
- 3. For Study 001, provide information regarding the frequency of systemic corticosteroid administration for all adverse events, immune-related AEs (all irAEs and by type of irAE) and infusion reactions. State the percentage of patients in each of the three categories who received high-dose steroids (> 40 mg prednisone equivalent), who were able to subsequently continue avelumab treatment and who had recurrence of the AE with subsequent exposure to avelumab. A table presentation would be acceptable.**

Please confirm receipt of this e-mail. Thank you.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
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/s/

IDARA UDOH
01/26/2017

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, January 24, 2017 3:57 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review. Our clinical reviewer has the following comments, and requests a response no later than **COB January 31, 2017**:

- 1) Provide a list of patients in Study 003 who had a temporary discontinuation of avelumab for an adverse event followed by a permanent discontinuation at a later date (for any reason) but never restarted avelumab after the temporary interruption. Comment on whether the initial adverse event which led to temporary interruption contributed to the subsequent permanent discontinuation. Also state whether or not the adverse event was immune-mediated. For example, for patient 9560001 who experienced an immune-mediated nephritis, we consider this adverse drug reaction to have led to permanent discontinuation of avelumab given that the patient had an interruption of dosing for grade 2 nephritis and then permanently discontinued avelumab at a later date for grade 1 elevated creatinine which was most likely the consequence of the immune-mediated nephritis. A summary table would be acceptable.
- 2) With regard to the incidence rates of adverse reactions causing temporary discontinuation of avelumab, please confirm that the only infusion-related reactions that were excluded from the overall incidence were those in which the avelumab infusion was temporarily interrupted and restarted at a reduced rate on the same day. Any other temporary discontinuation for an infusion reaction should be included in the overall incidence rate of adverse reactions leading to temporary discontinuation.
- 3) Please provide the medwatch report and a narrative for patient 9010001 that describes the ileus event that led to permanent discontinuation of avelumab during Study 003. The narrative in the CSR only describes the immune-mediated enterocolitis and diabetes adverse reactions in this patient.

Please submit your response formally to BLA761049, by the date specified above, in addition to providing a courtesy copy to me via email.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993

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/s/

IDARA UDOH
01/24/2017

Patel, Anuja

From: Patel, Anuja
Sent: Wednesday, January 18, 2017 7:27 AM
To: Virginia Pappalardo
Cc: Udoh, Idara
Subject: Clinical Information Request: BLA 761049/ EMD Serono/ Bavencio (avelumab)

Importance: High

Hello Virginia,

I am writing to you on behalf of your Regulatory Contact, Idara Udoh who is currently out of the office.

We refer to your BLA application for avelumab which is currently under our review.

Our clinical team has the following request for additional information and requests a response to be formally submitted to the BLA no later than January 25, 2017. Please email me (CC: Idara Udoh) a courtesy copy of the response.

- 1. Please provide information on all patients from Study 003 who were treated beyond radiologic progression. State the subject ID, the reason for continuing treatment, and the outcomes (e.g., a subsequent response, progressive disease, eventual discontinuation). Provide relevant dates and durations of any response that developed after progression. A table format would be acceptable. Also submit the case report forms for these patients.**
- 2. Provide a summary table of all patients who received corticosteroids during Study 003. Include the subject ID, the adverse event (or other reason) leading to steroid administration, whether the AE was considered related to avelumab, the specific steroid medication administered, the formulation, whether it was “high-dose” steroid therapy or not, duration of treatment, action taken with regard to study drug (continued, interrupted or discontinued), the AE outcome and whether there was recurrence if the patient continued to receive avelumab after the event.**
- 3. For Study 001, provide information regarding the frequency of systemic corticosteroid administration for all adverse events, immune-related AEs (all irAEs and by type of irAE) and infusion reactions. State the percentage of patients in each of the three categories who received high-dose steroids (> 40 mg prednisone equivalent), who were able to subsequently continue avelumab treatment and who had recurrence of the AE with subsequent exposure to avelumab. A table presentation would be acceptable.**

Please confirm receipt of this e-mail. Thank you.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎301.796.9022 (phone)

anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
01/18/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 01/13/2017 10:52:45 AM

To: virginia.papalardo@emdserono.com

CC: truong.quach@fda.hhs.gov; Idara.Udoh@fda.hhs.gov

BCC:

Subject: INFORMATION REQUEST BLA 761049

Dear Virginia,

Please see the attached microbiology IR. We request a response by January 25, 2017.
Kindly confirm that you have received this email communication.

Thank you.

Truong Quach, Pharm.D.

Regulatory Business Process Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research, FDA

10903 New Hampshire Ave, Building 75, Room 4620

Silver Spring, MD 20993



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We also refer to your amendment dated 04 November 2016 submission, containing your response to our Microbiology IR.

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **25 January 2017**.

We have the following Microbiology information request:

1. Labeling

The microbiological challenge study data does not support twice the label's recommended storage period of (b) (4) for the 0.9% or 0.45% sodium chloride solution diluted drug product. At 15 hour time point, *P.aeruginosa* and *E.coli* exhibited significant growth, a log₁₀ increase of > 0.5 reached 4.0 at 72 hour time point. Lack of growth at twice the post-dilution storage duration (b) (4) was not demonstrated. Please reduce the post-dilution storage period for the 0.9% or 0.45% sodium chloride solution diluted drug product to "not more than 4 hours" at room temperature.

2. Drug product manufacturing process

- a. Submit the protocol for the (b) (4) process step.

- b. Clarify and confirm that (b) (4) in the event of bioburden action limits are exceeded. In addition, indicate if additional bioburden samples will be taken (b) (4).

(b) (4)

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

Truong
Quach
-S

Digitally signed by
Truong Quach -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Truong Quach -S,
0.9.2342.19200300.100.
1.1=2001511949
Date: 2017.01.13
10:44:46 -05'00'

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Mid-Cycle Meeting Summary
December 8, 2016

Objectives

Succinctly present key findings of all reviews and inspections; identify any issues that could preclude an approval action; discuss labeling, PMCs/PMRs, and REMS; revise review plan, if needed; and develop plan for the Mid-Cycle Communication.

BLA: 761049, Type 1 New Molecular Entity

Rolling Submission:

- **Nonclinical eCTD submission—SDN 1 (received July 6, 2016)**
- **CMC eCTD submission—SDN 3 (received September 2, 2016)**
- **Clinical eCTD submission—SDN 4 (received September 23, 2016)**

Product: avelumab (MSB0010718C), injection for intravenous use, 20 mg/mL

Proposed Proprietary Name: Bavencio

Submission Date: September 23, 2016

Received Date: September 23, 2016

Sponsor: **EMD Serono, Inc.**

Proposed Indication: Treatment of patients with metastatic Merkel Cell Carcinoma (mMCC)

1. Application Milestone:

Milestone	Priority review 8-month PDUFA review	Comments
Application Received	September 23, 2016	
Filing Meeting (Day 30)	Tuesday, November 8, 2016	
Filing Action Letter (Day 60)	Tuesday, November 22, 2016	
Mid-Cycle Meeting	Thursday, December 8, 2016	
Hold Post Mid-Cycle Communication With Sponsor	Planned Target Date: TBD	Actual Goal Date: Saturday, January 7, 2017
Send proposed labeling/PMR/PMC/REMS to applicant (with 1 week response)	Planned Target Date: TBD	Actual Goal Date: Thursday, February 23, 2017
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Planned Target Date: TBD	Actual Goal Date: Thursday, March 2, 2017
Late Cycle Meeting	Planned Target Date: Thursday, March 23, 2016	Actual Goal Date: Thursday, March 23, 2017

Milestone	Priority review 8-month PDUFA review	Comments
Hold Wrap-Up meeting	Planned Target Date: Friday, April 14, 2016	Actual Goal Date: Tuesday, April 18, 2017
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	Planned Target Dates: Thursday, February 23, 2017 Saturday, February 25, 2017 Tuesday, April 25, 2017 Friday, May 12, 2017 Tuesday, May 23, 2017	Actual Goal Dates: Thursday, February 23, 2017 Saturday, February 25, 2017 Issue Disciplinary Review letters (as needed) by February 26, 2017 Tuesday, April 25, 2017 Saturday, May 13, 2017 Tuesday, May 23, 2017
Compile and circulate Action Letter and Action Package	Planned Target Date: TBD	Actual Goal Date: Tuesday, May 2, 2017
REMS Finalized; DRISK Review of REMS Finalized	Planned Target Date: TBD	Actual Goal Date: Tuesday, May 9, 2017
FINAL Action Letter Due	Planned Target Date: Tuesday, May 23, 2017	Actual Goal Date: Tuesday, May 23, 2017
Post Action Timeline		
Send action letter (fax or e-mail) to applicant and confirm receipt; notify Press Office if necessary	Planned Target Date: Tuesday, May 23, 2017	Actual Due Date: Tuesday, May 23, 2017
Send approval letter and summary review to FOI	Planned Target Date: Wednesday, May 24, 2017	Actual Due Date: Wednesday, May 24, 2017
Complete Action Pkg, send to DDR/FOI	Planned Target Date: Thursday, May 25, 2017	Actual Due Date: Thursday, May 25, 2017
Post-Action Feedback Meeting/End of Review Conference (if requested by Applicant)	TBD	TBD

2. Upcoming Internal Team Meetings

- **Labeling Meetings:** see schedule below. FDA sent PI with comments for EMD Serono's review on November 22, 2016; due December 13, 2016.

Meetings	Discipline Required	Label Sections	Date/Time/Location
#1	CMC, DMEPA, Clinical	3, 11, 16 and carton and container labeling	Mon 1/9/2017 12-1 PM WO22/Rm 2327
#2	Clinical, Statistics	1, 14	Thur 1/12/2017 12-1 PM WO22/Rm 3266
#3	DMEPA, Clinical	2, 7, 8.5, 8.6, 8.7, and 6.2 (Immunogenicity)	Tues 1/17/2017 2-3 PM WO22/Rm 2376
#4	Non-clinical, Clinical	12, 13, 8.1-8.4, 5 (if warning for embryo-fetal toxicity)	Thur 1/19/2017 12-1 PM WO22/Rm 2376
#5	Clinical	6	Mon 1/23/2017 12-1 PM WO22/Rm 2327
#6	Clinical	4, 5, 2, 17	Tues 1/24/2017 10-11:30 AM WO22/Rm 2327
#7	Clinical Pharmacology	12.2, 12.3	Fri 1/27/2017 10-11:30 AM WO22/Rm 2327
#8	All review disciplines	Any items not covered during originally scheduled time	Tues 1/31/2017 2-3 PM WO22/Rm 3270

- **Team Meetings:**

Meetings	Date	Comments
January 2017	Wed 1/11/2017; 1-2 PM; WO 22, Room 4201	
February 2017	Tues 2/7/2017; 10-11 AM; WO 22, Room 3201	
March 2017	Mon 3/6/2017; 2-3 PM; WO 22, Room 3270	
April 2017	Mon 4/3/2017; 2-3 PM; WO 22, Room 3266	

1. Team Updates

- Clinical/Statistics

DISCUSSION: Updates provided in clinical slides.

- Clinical Pharmacology

DISCUSSION: Updates provided in clinical pharmacology slides. Dosing regimen appears reasonable.

- Nonclinical

DISCUSSION: Updates provided in nonclinical slides. No issues or post-marketing requirements or commitments (PMR/PMC) to date. Discussions regarding (b) (4) studies are ongoing.

- CMC (including manufacturing site inspection update)

DISCUSSION: Updates provided in product quality slides. Potential PMR/PMC have been identified. An information request regarding validation characteristics will be issued.

2. Information Request Status

- CMC
 - Microbiology quality, issued 11/29/2016, due 12/19/2016
 - Manufacturing, issued 11/30/2016, due 12/12/2016
- Clinical
 - CRF and AE, issued 12/5/2016, due 12/16/2016

3. Discussion on potential PMC/PMR or REMS:

- EMD Serono proposed the following PMR



(b) (4)

POST-MIDCYCLE DISCUSSION: Per 12/9/16 email from Dr. Summers, this proposal is considered a PMC, not a PMR, following recent discussions with the Safety Requirements Team regarding standard clinical pharmacology request.

- Have any other been identified?

DISCUSSION: The CMC reviewer has identified an additional PMR/PMC, [REDACTED] that is still under review and will be conveyed to the Sponsor in a later communication.

(b) (5)

4. Discussion on items to communicate to sponsor during the Post Mid-Cycle Communication:

- Key issues/deficiencies and need for additional information?
 - Who will convey the deficiencies/information?
 - What will be the order in which the deficiencies/information will be provided?
- PMR/PMC and REMS issues?
- REMINDER: Post mid-cycle communication agenda due to EMD Serono two days prior to communication meeting

5. Consult Status

OPDP	Nicholas Senior/Trung-Hieu (Acting)
OSE	DMEPA: Janine Stewart, DMEPA Reviewer/Alice Tu DRISK: Naomi Redd
OSI	Lauren Iacono-Connor/Susan Thompson
QT-IRT	Janell Chen/Mike Li
DMPP (Patient Labeling)	Morgan Walker/Barbara Fuller

6. MISC Items or Issues

- REMINDER: this application is under the shared review pilot
 - Pertains to clinical, nonclinical, clinical pharmacology & DDS/sRPM
 - Sharepoint Location: [Multidisciplinary Review BLA761049](#)
- Any other issues?

7. Review Action Items and Decisions

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/s/

IDARA UDOH
01/06/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 01/04/2017 12:53:40 PM
To: virginia.pappalardo@emdserono.com
CC: truong.quach@fda.hhs.gov
BCC:
Subject: INFORMATION REQUEST BLA 761049

Dear Ms. Virginia,

Please see the attached IR letter. We request a response by January 10, 2017. Kindly confirm that you have received this email communication.

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Ave, Building 75, Room 4620
Silver Spring, MD 20993



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **10 January 2017**.

We have the following information request:

3.2. S.2.3.3 Cell Banking System, Characterization, and Testing

(b) (4)

3.2. S.4.1 and 3.2.P.5.1 Specifications

2. *We require additional justification or modifications to your proposed specifications to ensure the ranges proposed for the following product quality attributes do not result in a meaningful change in product quality. Additionally, upon revision of your specifications, please revise ongoing stability protocols to reflect these revisions.*

- a. *The acceptance criterion for basic group- charge variant differs from clinical experience and insufficient information is provided to assess the impact of basic variants at the highest numerical value you propose. Provide additional justification or alter your proposed criteria to (b) (4) %.*
- b. *As you propose ADCC as a secondary mechanism of action, control of glycosylation is critical. Provide justification that ADCC activity would be appropriately controlled for the a-fucosylated complex glycan range you propose. Alternatively, you may consider revising your specification to (b) (4) %.*
- c. *We propose to revise potency acceptance criteria for both DS and DP to (b) (4) % given both clinical and manufacturing experience, and the observation that the method is considered stability indicating.*
- d. *The deamidation characterization summary provided in Figure 44 in section 3.2.S.3.1 suggests that deamidation results in an increase in potency. This observation is further corroborated by stability under accelerated conditions. Consequently, we do not agree that your justification for (b) (4) is justified based on data provided. We propose you modify your specification for drug product to: NMT (b) (4) % (release), NMT (b) (4) % (stability).*
- e. *We are unclear how the presence of new bands in purity assays (reducing and non-reducing CE-SDS) would be controlled based on the specifications provided. You should include a criterion that state that no new bands or peaks are allowed. This should also be included in your reference standard protocol # 20243761.*
- f. *In your IR response dated December, 9 2016 to question 12, you indicate that the specification provided reflects criteria established for evaluating drug product at the end of shelf life. The specification for drug substance and drug product should clearly state and highlight any differences in release and stability criteria.*

3.2. S.7.2 and 3.2.P.8.2. Post approval stability protocol and stability commitment

3. *Include a test to assess aggregates in your post approval stability protocols for both DS and DP with equivalent criteria to those in you proposed specifications.*

3.2. S.7.3 and 3.2. P.8.3 Stability data

4. *Provide a stability update for process validation batches of both DS and DP to aid in comparison of their stability profiles relative to your primary programs.*
5. *The quantity of leachable and extractables data for drug substance and drug product (15 months at long-term storage) would not be sufficient to extend the shelf life of either upon the availability of subsequent stability data points. If you intend to extend shelf life based on these protocols, they should be updated to include assessment for leachables on an annual basis.*

5.3.1.4 Reports of bioanalytical and analytical methods for human studies

6. *You stated in your IR response dated December 23, 2016 that you intend to re-analyze all samples using the cut point obtained from treatment naïve patient samples in the screening assay and would test all positive samples in the confirmatory assay to determine the titer. Provide an estimate for when this updated analysis would be available.*

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

Truong
Quach -
S

Digitally signed by Truong
Quach -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Truong Quach -S,
0.9.2342.19200300.100.1.1
=2001511949
Date: 2017.01.04 12:48:11
-05'00'

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Udoh, Idara

From: Udoh, Idara
Sent: Friday, December 16, 2016 8:06 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good evening, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review.

We also refer to your December 7, 2016, amendment containing information on IRC-determined response duration from the 12 month exploratory analysis on the N=88 ITT population from Study EMR100070-003; your December 13, 2016, amendment containing clean and redlined package inserts in Word and PDF formats for avelumab; and your December 14, 2016, amendment containing your response to our December 5, 2016 information request.

Our clinical reviewer has the following comments, and requests a response at the time of submitting your 90-day safety update:

- 1) We note that 88% of patients (n=77) in Study 003 experienced anemia during treatment with avelumab, 15% of patients (n=13) experienced anemia as an adverse event and that 10% of these patients (n=9) experienced $\geq$ grade 3 anemia. Anemia was considered related to study drug in only one of the 13 patients. Provide a summary table of the 13 patients who experienced an adverse event of anemia during treatment and include columns for age, baseline hemoglobin, lowest hemoglobin while on treatment, days from initiation of avelumab to start of the adverse event, duration, concomitant medications, any dose modifications or medical interventions that took place for the anemia, and a causality assessment if the event was considered unrelated to avelumab treatment. Comment on the incidence of anemia with avelumab as compared to other available PD-1 inhibitors.
- 2) Provide an updated analysis of myositis and myocarditis in the 90 day safety update. State the incidence rate of myocarditis across the avelumab development program and describe the pooled databases that have been queried (Study 001, 003, ARISg and any others). Include the narratives for the four patients with myocarditis described in the Summary of Clinical Safety and any additional narratives for events that occurred up until the later data cutoff in your analysis.

Additionally, if you plan to update the efficacy and safety information in the avelumab product label based on the results of analyses conducted when all patients had been followed for at least 12 months from enrollment, please submit the modified proposed labeling (clean and tracked changes versions) with the 90 day safety update.

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager

Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
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idadara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
12/16/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/15/2016 11:18:08 AM

To: virginia.pappalardo@emdserono.com

CC: Idara.Udoh@fda.hhs.gov, truong.quach@fda.hhs.gov

BCC: Arulvathani.Arudchandran@fda.hhs.gov

Subject: INFORMATION REQUEST BLA 761049

Dear Ms. Pappalardo,

I've attached another CMC IR and request a response by December 23, 3016. Please confirm that you have received this email communication.

Thank you.

Truong Quach, Pharm.D.

Regulatory Business Process Manager

Office of Program and Regulatory Operations

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research, FDA

10903 New Hampshire Ave, Building 75, Room 4620 Silver Spring, MD 20993



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **23 December 2016**.

We have the following information request:

5.3.1.4- reports of bioanalytical and analytical methods for human studies:

1. Provide a justification for the use of (b) (4) rather than untreated patient samples for the determination of the cutpoint for the screening and confirmation assays for the determination of anti-drug antibodies. This justification should include an assessment of the calculated false positive rate relative to the rate of treatment naïve patients who tested positive in both the screening and confirmatory portion of the assay.
2. It is noted that page 15 of the validation report for the "Validation of Analytical Method for the Detection of Antibodies to Anti-PDL1 in Human Serum by Meso-Scale Discovery Electrochemiluminescence (ECL)" states "Additional testing of the screening cut point and selectivity will be performed using patient pre-dose samples from an on-going clinical trial when available and will be reported as an addendum." Provide this data.

3. Clarify any differences in the immunogenicity methods for determination of ADA in studies EMR 100070-001 and 100070-003, (b) (4).
4. The BLA Submission includes a method, Qualification of the Immunoassay Method PBTM-131 for the Detection of Binding Antibodies Anti MSB0010718C (Anti-PD-L1) in Human Serum: Long Term Stability." Clarify the use of this method and testing site in your immunogenicity assessment program.
5. Provide data to support that the biotinylated avelumab concentration is used at the optimal concentration to capture ADAs in the screening and confirmatory assays.
6. Describe the details for the methods used to assess the robustness and provide data to support the robustness of the Method- TLIAM-13170 that is used to quantify the treatment-related ADA incidence.
7. Provide a description and justification to demonstrate that the method used to eliminate outliers is appropriate and would result in a normal distribution of the data. Provide this information for the cutpoint determination for both the screening and confirmatory assays.

3.2. P.7- container closure:

8. The proposed labeling states that avelumab drug product should be protected from light. However, detail is not provided in this section to describe the secondary container closure. Provide this additional detail. Additionally, provide sufficient justification that it provides adequate protection throughout the shelf life.

3.2.P.2.6 – Compatability:

9. You propose to use (b) (4) diluent for administration of avelumab. Provide additional justification to support your omission of the evaluation of this diluent from your administration simulation study.
10. In Table 22, a large percentage of LMW% were observed for each sample measured at a protein concentration of 0.016 mg/mL. Provide additional information regarding these elevated levels, including any characterization as well as an assessment for their impact on product performance.
11. It is noted that oxidation was excluded from your compatability study to demonstrate that dilution and administration does not affect product quality attributes. However, oxidation has been demonstrated to be a potential pathway of degradation. Provide data for the assessment of oxidation of the diluted DP to support the stability prior to the administration under clinical setting.

3.2.P.3.5- process validation- shipping validation for DP

12. Data submitted in support the validation of the shipping of DP is not adequate.

Provide the following:

- a. A justification for the exclusion of potency from your assessment of the effect of shipping on drug product performance
- b. A description for how the time for maximum shipping time is controlled during routine shipment
- c. An assessment on the degree to which shipping load may affect product quality attributes
- d. Clarify whether you have a statement in the attached label that indicates the requirement of the storage of DP (b) (4) at the receiving facility.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Truong
Quach

Digitally signed by Truong Quach

Date: 12/15/2016 11:09:08AM

GUID: 5407887a000a1c163198a394481b0ee6

Udoh, Idara

From: Udoh, Idara
Sent: Monday, December 05, 2016 11:34 AM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good morning, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review.

Our clinical reviewer has the following comments, and requests a response to this information request by noon, **Friday, December 16, 2016:**

- 1. It is our understanding that a total of 1437 patients were enrolled in the expansion phase of Study 001 and that this group, combined with the 15 patients treated during the dose-escalation phase of Study 001 with avelumab 10mg/kg, comprise the 1452 patients in the Study 001 safety population. During review of the datasets corresponding to Study 001, it was noted that the ADAE dataset (Section 5.3.5.2, Analysis Dataset Adam) for the expansion phase of Study 001 includes only 1429 unique patients and that only 1365 of these patients received at least one dose of study drug (i.e., SAFFL=Y). Although we can confirm the absolute numbers of adverse events as reported in the Summary of Clinical Safety, the incidence rate changes based on the different denominator. Please explain why this dataset does not include all 1437 patients who received at least one dose of avelumab during the dose expansion phase of Study 001. Alternatively, if there is another AE dataset corresponding to the expansion phase of Study 001 in the application, provide the location.**
- 2. Provide one adverse event dataset that includes all patients who received at least one dose of avelumab 10mg/kg during Study 001 (n=1452).**
- 3. Submit the Case Report Forms (CRFs) for the three patients enrolled in Study 003 whose cause of death was reported as “unknown” (Subject IDs 1020001, 1050003 and 2040007). If you have any updated information regarding these deaths, provide this as well.**

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)

idara.udoh@fda.hhs.gov (email)

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

/s/

IDARA UDOH
12/05/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/30/2016 02:03:31 PM

To: virginia.pappalardo@emdserono.com

CC: Idara.Udoh@fda.hhs.gov; truong.quach@fda.hhs.gov

BCC:

Subject: INFORMATION REQUEST BLA 761049

Dear Ms. Pappalardo,

I apologies for the multiple IR request, but we have another inquiry. Please see the attached IR letter and provide a response by December 12, 2016 if possible.

Thank you for your time.

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Ave, Building 75, Room 4620
Silver Spring, MD 20993



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We also refer to your 23 September 2016 submission, containing the rolling Biologics License Application (BLA) seeking approval for avelumab, a fully human immunoglobulin (Ig) G1 monoclonal antibody directed against PD-L1.

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **12 December 2016** and update the information in the appropriate modules of the BLA.

We have the following CMC Information Request:

Manufacturers (3.2.S.2.1)

1. *We note that both Merck Serono S.A. (Aubonne Switzerland) and Merck Serono S.p.A. (Guidonina Montecelio) is intended as drug substance testing sites. Provide additional detail on which site performed analytical method validation, as well as the qualification strategy (e.g., covalidation or method transfer) for the remaining site.*

Description of Manufacturing (3.2.S.2.2)

2.

(b) (4)

(b) (4)

Container Closure System (3.2.S.6.1)

10. We require additional information to evaluate the adequacy of your extractable and leachables study. Please provide the following:

- a. We note that you state that no inorganic compounds were detected. Provide additional information on the quantitation limits used to establish this threshold.
- b. You state that [REDACTED] (b) (4). Provide additional information on the identity of these species and a risk assessment for their impact on product performance.

Specifications (3.2.S.4.1 and 3.2.P.5.1)

11. We do not agree with the approach to establish acceptance criteria based [REDACTED] (b) (4). Your proposed limits and justification should reflect the impact of each individual critical quality attribute on product performance and where possible, actual clinical experience. In particular we ask for additional justification for the proposal of the acceptance criteria of the following tests:

- a. *Charge Variant Profile*
- b. *Glycosylation Profile (Drug Substance only)*
- c. *Potency*
- d. *HMW Species*
- e. *Low Molecular Weight Species*
- f. *Electrophoretic Purity*
- g. *Oxidation*
- h. *Deamidation*

12. *Clarify whether the specifications listed in Table 1 of section 3.2.P.5.1 are intended for stability or are only assessed for release.*

Analytical Methods and Analytical Method Validation (3.2.S.4.3 and 3.2.S.4.4)

13. *Provide a summary description of the assay and the source (in-house or commercial) of the antiserum used for detection of host cell protein impurities (HCPs). The anti-HCP antiserum needs to be qualified for its ability to detect potential HCP impurities. This assessment should include 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis using the antiserum employed in the assay. It is possible to use a similarly sensitive and discriminating assay in lieu of the 2D SDS-PAGE assay. If an alternative pathway is pursued, consultation with the Agency is recommended. These data should be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum. It is the agency's experience that analysis of HCP coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently informative for this purpose.*

14. *The proposed identification tests (SE-HPLC and iCE) did not include data in their respective validations that they are sufficient to discriminate between other products manufactured at the same facility. Provide additional data that demonstrate the tests provide sufficient discriminatory power.*

15. *We require additional data to understand the routine performance of your analytical procedures and if their validation was performed consistent with ICH Q2(R1) guidelines. Provide the following additional information:*

- a. *For the iCE method:*
 - i. *data supporting the robustness of the method to changes in capillary column batches and temperature*
 - ii. *Additional information for how temperature is controlled during routine performance*
- b. *For the 2-AB glycan mapping:*
 - i. *Data to demonstrate robustness relative to parameters for enzyme digestion to release glycan species, labeling efficiency with fluorephore 2- aminobenzamide, individual column batches, temperature, and buffer conditions.*
- c. *For the Optical density:*
 - i. *Clarification for Table 22 which states the comparison is between matrix B and water though the data table suggests matrix B and matrix A.*
- d. *For the Cell binding assay:*
 - i. *Clarification if the evaluation of precision included data for different analysts and different batches of plates used.*
- e. *For the CE-SDS:*
 - i. *Additional information for the root cause analysis for the instrument failure during the validation and its successful resolution in the current QC environment*
- f. *For the Host cell protein assay:*
 - i. *data supporting the robustness of the method to changes different batches of ELISA plates, concentration of (b) (4) antibodies*
- g. *For the SE-HPLC method:*
 - i. *Justification for the exclusion of a resolution criteria for aggregates from system suitability*

16. Provide an updated batch analysis table which includes both Process B material and Process A material used in clinical trials. Where differences in methods used for release provide clarification and reference to bridging data that support that the methods used have equivalent performance.

Drug Product Manufacture (3.2.P.3.2)

17. Provide additional detail on the limits of the (b) (4) and document the information in the SOP.

18. Provide information to confirm that identity testing of avelumab as per 21 CFR 610.14 that states an identity test must be performed on products after all labeling operations have been completed.

Drug Product Control of Critical Steps and Intermediates (3.2.P.3.4)

19. Provide information of the number (b) (4) under the maximum and minimum conditions.

We are unclear how the (b) (4) is monitored throughout the course of routine manufacturing. Provide additional detail describing the (b) (4) during drug product manufacture.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

Truong
Quach -S

Digitally signed by Truong
Quach -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Truong Quach -S,
0.9.2342.19200300.100.1.1=2
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Date: 2016.11.30 14:02:33
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Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 11/29/2016 11:32:44 AM

To: virginia.pappalardo@emdserono.com

CC: truong.quach@fda.hhs.gov; idara.udoh@fda.hhs.gov

BCC: truong.quach@fda.hhs.gov

Subject: INFORMATION REQUEST BLA 761049

Dear Ms. Pappalardo,

Please see the attached CMC information request. We request a response by December 19, 2016. Please confirm that you have received this email communication.

Thank you,

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Ave, Building 75, Room 4620
Silver Spring, MD 20993



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We also refer to your 23 September 2016 submission, containing the rolling Biologics License Application (BLA) seeking approval for avelumab, a fully human immunoglobulin (Ig) G1 monoclonal antibody directed against PD-L1.

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **19 December 2016**.

We have the following microbial quality for drug substance information request:

Manufacture - Description of the Manufacturing Process and Process Controls

1. Your manufacturing process uses (b) (4). Indicate how endotoxin levels are controlled in (b) (4) and provide endotoxin and bioburden limits of (b) (4).
2. Please confirm that the (b) (4).

Manufacture - Control of Critical Steps and Intermediates

(b) (4)

(b) (4)



If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Truong
Quach

Digitally signed by Truong Quach
Date: 11/29/2016 11:17:27AM
GUID: 5407887a000a1c163198a394481b0ee6



BLA 761049

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

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(a) of the Public Health Service Act for Bavencio (avelumab) injection, for intravenous use, 20 mg/mL.

We also refer to your rolling review pre-submissions received on July 6, 2016; September 2, 2016, and your amendments submitted on August 22, 2016; October 17, 2016; October 20, 2016; October 27, 2016; October 28, 2016; November 4, 2016; November 11, 2016; November 15, 2016; and November 16, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is May 23, 2017.

This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 23,

2017. In addition, the planned date for our internal mid-cycle review meeting is December 8, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues. Please provide responses to the review issues identified below, within 30 days from the date of this letter.

Drug Product Quality Microbiology:

1. Provide data to support the proposed labeling claim that drug product diluted in 0.9% or 0.45% sodium chloride solution may be stored refrigerated at 2- 8°C (36- 46°F) (b) (4) for up to 24 hours, as no microbiological data to support the proposed claim is provided in the application.
2. Provide the appropriate Letter of Authorization (LOA) from the vial stopper manufacturer to the CDER Drug Master File (DMF) to support that the proposed vial stoppers are (b) (4) and that the validation data to support the (b) (4) vial stopper is located in that CDER DMF. The letter should specify the date of submission of the cross-referenced information and, if appropriate, the volume and page numbers within that submission.
3. Provide summary data or a report of filter manufacturer's sterilizing filter integrity test study performed using the product.
4. Provide information and summary data of the three recent (b) (4) for the vials.
5. Provide information and summary data from the three recent requalification runs of (b) (4) sterilization including biological indicator (BI) information (BI type, expiry, D-value, population, confirmed population and incubation conditions).
6. Provide information and summary data from the initial and two additional recent requalification runs of (b) (4) information used for the (re)qualification runs.
7. Provide a description of the (b) (4) drug product contact equipment and components including (b) (4) used during validation.
8. Provide summary data and information on the validation of the (b) (4) including acceptance criteria, (b) (4)

9. Provide (b) (4) validation data summaries for the (b) (4) including the (b) (4) audit report.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We also have the following request for additional information. Provide the requested information in an amendment to your BLA within one week from the date of this letter.

10. During the November 7-15, 2016 pre-licensing inspection of the Merck Serono SA facility proposed for avelumab drug substance manufacture, the investigators determined that the site for mycoplasma testing, (b) (4) is not listed in your 356h form or Module 3.2.S.2.1. Please add (b) (4) to the 356h form and include the site information in Module 3.2.S.2.1. In addition, please provide *all* FEI numbers for *all* facilities listed in Modules 3.2.S.2.1 and 3.2.P.2.1.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified labeling issues and have included our labeling comments and questions for you to address in the attached labeling.

We request that you resubmit labeling (in both clean and redlined (track-changes shown) Microsoft Word format) that addresses these issues and our questions by December 13, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to

correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 601 Subpart E – *Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 601.45, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (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>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

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 the biological product for this indication has orphan drug designation, you are exempt from this requirement.

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

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
FDA comments/proposed revisions to labeling

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA KEEGAN
11/22/2016

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, November 15, 2016 8:41 AM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Patient Labeling): BLA761049/EMD
Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good morning, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review.

We acknowledge receipt of your proposed Medication Guide, in PDF format. Please provide this document in a Word version. If the Medication Guide is already included in the application in the Word version, please provide the location.

We request a response by **COB November 15, 2016**, via courtesy email to me and formal submission to BLA 761049. Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

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/s/

IDARA UDOH
11/15/2016

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, November 08, 2016 3:01 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Ms. Pappalardo. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review.

We acknowledge submission of the financial disclosure information in module 1.3.4 including the FDA 3454 and 3455 forms and the attached tabular lists of investigators who participated in studies supporting the BLA; however, for those investigators for whom financial disclosure information is missing, please submit certification that you acted with due diligence but were unable to obtain this information (FDA form 3454, option 3). Provide the reason why this information was not able to be obtained. If this information is already included in the application, please provide the location.

We request a response by **COB November 15, 2016**, via courtesy email to me and formal submission to BLA 761049. Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 22, Room 2365
Silver Spring, MD 20993
301.796.3074 (phone)
301.796.9849 (fax)
idara.udoh@fda.hhs.gov (email)

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

/s/

IDARA UDOH
11/15/2016

**Initial Planning Meeting Summary
October 17, 2016**

BLA: 761049, Type 1 New Molecular Entity

Rolling Submission:

- **Nonclinical eCTD submission—SDN 1 (received July 6, 2016)**
- **CMC eCTD submission—SDN 3 (received September 2, 2016)**
- **Clinical eCTD submission—SDN 4 (received September 23, 2016)**

Product: avelumab (MSB0010718C), injection for intravenous use, 20 mg/mL
Proposed Proprietary Name: Bavencio
Submission Date: September 23, 2016
Received Date: September 23, 2016
Sponsor: EMD Serono, Inc.

Proposed Indication: “Treatment of patients with metastatic Merkel Cell Carcinoma (mMCC)”

Meeting Attendees:

Division Signatory

Patricia Keegan, Director, Division of Oncology
Products 2 (DOP2)

Project Management

Norma Griffin, Team Leader
Idara Udoh, Sr. Regulatory Project Manager (RPM)
Anuja Patel, Sr. RPM

Clinical

Suzanne Demko, Clinical Team Leader
Denise Casey, Clinical Reviewer

Nonclinical

Whitney Helms, Non-Clinical TL

Clinical Pharmacology

Jeanne Fourie-Zirkelback, Clin Pharm TL
Safaa Burns, Clin Pharm Reviewer

Regulatory Background

Fast Track Designation was granted for avelumab on October 1, 2015, for the treatment of metastatic Merkel cell carcinoma (mMCC) to demonstrate a clinically important and statistically robust improvement in progression free survival (PFS) for patients treated with avelumab compared to available therapy.

Breakthrough Therapy Designation was granted for avelumab on November 17, 2015, for the treatment of patients with mMCC that have progressed after at least one previous chemotherapy regimen.

Biometrics

Pallavi Mishra-Kalyani, Biometrics Reviewer

Product Quality (OBP)

Joel Welch, OBP-ATL
Arulvathani Arudchandran, OBP Reviewer
Lakshmi Narashmhan, DMA-DP

OSE

Latonia Ford, Safety RPM
DRISK: Naomi Redd, Risk Management Reviewer
Pharmacovigilance: Shaily Arora

Pharmacometric

Nan Zheng
Jiang Liu

Discipline-specific pre-BLA meetings were held prior to the multidisciplinary pre-BLA meeting, which was held on June 16, 2016, to discuss and reach agreement on the content and format of the planned BLA for avelumab, and to discuss and reach agreement on the design of the trial intended to confirm clinical benefit. The discipline specific meetings are listed below:

- Clinical pharmacology, held April 15, 2016
- CMC, held April 26, 2016
- Nonclinical (written responses), issued June 8, 2016

Request for proprietary name review of Bavencio was submitted August 22, 2016. Review is currently pending.

A Type B, pre-BLA meeting was held on June 16, 2016 between FDA and EMD Serono under IND 119394 to discuss and reach agreement on the content and format of their planned BLA for avelumab, and to discuss and reach agreement on the design of the trial intended to confirm clinical benefit. Meeting minutes from this meeting issued on July 6, 2016. A separate CMC only meeting was held April 26, 2016 and meeting minutes were issued May 24, 2016.

Agenda Items:

1. **Review Status: PRIORITY 8 Month Review (Goal Date Tuesday, May 23, 2017)**
 - a. Completed BLA (September 23, 2016 submission) contained the following requests:
 - Priority review
 - Patent and Exclusivity—Exclusivity for the “first licensure” of avelumab, for the treatment of patients with metastatic Merkel cell carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen.
 - Environmental Analysis—Categorical Exclusion requested
 - Risk Management Plan—Proposed PMR milestone and planned assessment
 - b. Orphan Drug Designation – Granted on September 21, 2015
 - c. Proprietary Name Review- Conditional acceptance granted April 28, 2016

2. **Dates Milestone Letters Must Issue**

Milestone	Priority review 8-month PDUFA review	Comments
Application Received	September 23, 2016	
Acknowledgment Letter	Planned Target Date: October 7, 2016	Issued October 14, 2016
Planning/Kickoff Meeting (Day 30)	Planned Target Date: Sunday, October 23, 2016	Scheduled Monday, October 17, 2016
Filing Meeting (Day 30)	Planned Target Date: Sunday, October 23, 2016	Scheduled Tuesday, November 8, 2016

Milestone	Priority review 8-month PDUFA review	Comments
Filing Action Letter (Day 60) (Inform applicant of review designation, filing determination)	Planned Target Date: Tuesday, November 22, 2016	Actual Due Date: Tuesday, November 22, 2016
Deficiencies Identified Letter (74 Day Letter)	Planned Target Date: Tuesday, December 6, 2016	Actual Due Date: Tuesday, December 6, 2016
Hold Mid-Cycle Meeting	Planned Target Date: TBD	Actual Goal Date: Friday, December 23, 2016
Hold Post Mid-Cycle Communication With Sponsor	Planned Target Date: TBD	Actual Goal Date: Saturday, January 7, 2017
Send proposed labeling/PMR/PMC/REMS to applicant (with 1 week response)	Planned Target Date: TBD	Actual Goal Date: Thursday, February 23, 2017
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Planned Target Date: TBD	Actual Goal Date: Thursday, March 2, 2017
Late Cycle Meeting	Planned Target Date: TBD	Actual Goal Date: Thursday, March 23, 2017
Hold Wrap-Up meeting	Planned Target Date: TBD	Actual Goal Date: Tuesday, April 18, 2017
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i>	Planned Target Dates: Thursday, February 23, 2017 Saturday, February 25, 2017	Actual Goal Dates: Thursday, February 23, 2017 Saturday, February 25, 2017 Issue Disciplinary Review letters (as needed) by February 26, 2017

Milestone	Priority review 8-month PDUFA review	Comments
<i>CDTL Review Due</i>	Tuesday, April 25, 2017	Tuesday, April 25, 2017
<i>Division Director Review Due</i>	Friday, May 12, 2017	Saturday, May 13, 2017
<i>Office Director Review Due/Sign-Off</i>	Tuesday, May 23, 2017	Tuesday, May 23, 2017
Compile and circulate Action Letter and Action Package	Planned Target Date: TBD	Actual Goal Date: Tuesday, May 2, 2017
REMS Finalized; DRISK Review of REMS Finalized	Planned Target Date: TBD	Actual Goal Date: Tuesday, May 9, 2017
FINAL Action Letter Due	Planned Target Date: Tuesday, May 23, 2017	Actual Goal Date: Tuesday, May 23, 2017
Post Action Timeline		
Send action letter (fax or e-mail) to applicant and confirm receipt; notify Press Office if necessary	Planned Target Date: Tuesday, May 23, 2017	Actual Due Date: Tuesday, May 23, 2017
Send approval letter and summary review to FOI	Planned Target Date: Wednesday, May 24, 2017	Actual Due Date: Wednesday, May 24, 2017
Complete Action Pkg, send to DDR/FOI	Planned Target Date: Thursday, May 25, 2017	Actual Due Date: Thursday, May 25, 2017
Post-Action Feedback Meeting/End of Review Conference (if requested by Applicant)	TBD	TBD

Discussion During Meeting:

- 1) RPM will begin scheduling meetings listed as TBD. The mid-cycle meeting should be scheduled 2 weeks prior to actual goal date shown in table, due to the holidays and potential unavailability of reviewers.**
- 2) There is no need for REMS.**

3. **Potential Consults/Collaborative Reviewers Needed:**

OPDP	TBD, Consult to be submitted
OSE	Latonia Ford, OSE SRPM <u>DMEPA</u> Alice Tu (TL) <u>DRISK</u> - Naomi Redd, DRISK Reviewer
Maternal Health	Is consult needed?
OSI	Consult to be uploaded pending IR response, Lauren Iacono-Connor
Facility/OMPQ	Steven Fong, OBP Reviewer
Microbiology	No assignment provided
Biopharmaceutics	No assignment provided, is one needed?
QT-IRT	Consult submitted, September 19, 2016 Reviewers: Janell Chen Mike Li
Pediatric Page/PeRC	TBD, Consult to be submitted
Patient Labeling Team	TBD, Consult to be submitted
SGE's or Patient Representatives	Are SGEs Needed; contact Deb Miller, if patient representative is needed

Are there any additional consults needed?

Discussion During Meeting:

- 1) **No consults needed for the following:**
 - a. **DRISK, Maternal Health**
- 2) **All other items listed above require consultation, with exception of Facilities, Microbiology, and Biopharmaceutics, which are members of the review team and already have assignments.**
- 3) **OSE has requested that the Sponsor submit a Risk Management Plan to the BLA. Information Request to issue following the meeting, Pharmacovigilance reviewer will provide specific language.**
- 4) **RPM to forward current SGE list to clinical reviewer to determine whether disease specific SGEs can be identified.**

4. Upcoming/TBD Internal Team Meetings:

- a. **Filing Meeting:** Scheduled for Tuesday, November 8, 2016
- b. **Mid-Cycle Meeting:** TBD, anticipated for week of December 19, 2016

Discussion During Meeting:

1) No internal meeting to prepare for midcycle is needed.

c. Labeling Meetings (suggested section groupings):

EMD Serono submitted the following labeling in the application:

Draft PI Labeling (clean)

Carton/Vial: 200 mg/10mL (20 mg/mL, for intravenous infusion after dilution, single dose vial)

- **Date for communicating labeling/PMR/PMC to applicant is Thursday, February 23, 2017**
- **Please refer to attachment for schedule of proposed labeling meeting sections (by discipline)**

Discussion During Meeting:

1) RPM to start scheduling labeling meetings in the second week of January 2017, two meetings per week.

2) Clinical pharmacology requested that their labeling meeting be moved to a later time (preferably as Meeting 7 or 8), not as assigned in the attached “Labeling Meeting Organization and Scheduling for NME” document. This proposal was accepted.

d. Team Meetings and PMR/PMC Working Meetings:

- Previous communication of proposed PMR/PMC (Refer to April 18, 2016 clinical pharmacology meeting minutes)
 - o EMD Serono proposes the following PMR:



- Do we want to schedule monthly team meetings (OSE/DRISK)?

- Do we want to schedule any separate PMC/PMR meetings?

Discussion During Meeting:

1) RPM should wait until after the midcycle meeting to schedule any monthly team meetings or separate PMR/PMC meetings.

- e. **Late-Cycle Meeting:** Per 8 month clock, to be scheduled no later than March 23, 2017
 - Pre-meeting for late cycle meeting, to be scheduled no later than March 2, 2017
 - Send late cycle package to Sponsor by March 10, 2017
- f. **Wrap-Up Meeting:** Per 8-month clock, to be scheduled no later than Tuesday, April 18, 2017

5. Applicant Orientation Presentation:

Tuesday, October 18, 2016, 1:00 PM – 2:00 PM, EST; data sets meeting to follow, 2:00 PM-2:30PM, EST

6. ODAC Needed/Not Needed:

Discussion During Meeting:

1) No ODAC needed.

7. OBP Discussion

- a. Truong Quach is assisting with the following consults via Panorama:
 - Establishment (EES)/ Coordinate Inspections-

8. Miscellaneous Items or Issues:

- Do we need any preclinical study site audits?
- Since this is an NME, is Press Release and Burst planned?

Discussion During Meeting:

1) No need for preclinical study site audits:

2) Press release and Burst to be planned

3) OSE has requested that the Sponsor submit a Risk Management Plan to the BLA. Information Request to issue following the meeting, Pharmacovigilance reviewer will provide specific language.

4) RPM to forward current SGE list to clinical reviewer to determine whether disease specific SGEs can be identified.

9. Other Issues/Concerns

- **Do we need to schedule weekly or every other week tcons with the sponsor in case we have issues as reviews proceed?**
- **Any other IRs/Advice to Sponsor anticipated at this time, from any discipline?**

Discussion During Meeting:

- 1) **Biweekly update teleconferences between clinical team and EMD Serono can be scheduled starting mid-November 2016. Meetings will be cancelled if nothing to be discussed.**

APPEARS THIS WAY ON ORIGINAL

Labeling Meeting Organization and Scheduling for NME

Meeting Date	Discipline Attendance Required	Label Section(s) to be discussed	Length of Meeting
1 st meeting	CMC, DMEPA, Clinical	3, 11, 16 and carton and container labeling	1 hour
2 nd meeting	Clinical, Statistics	1, 14	1 hour
3 rd meeting	Clinical Pharmacology, DMEPA, Clinical	2, 7, 8.5, 8.6, 8.7, 12.2, 12.3 and 6.2 (Immunogenicity)	1.5 hours
4 th meeting	Non-clinical, Maternal Health Team (MHT), Clinical	12, 13, 8.1-8.4, 5 (if warning for embryo-fetal toxicity)	1.5 hours
5 th meeting	Clinical	6	1 hour
6 th meeting	Clinical	4, 5, 2, 17	1.5 hours
7 th meeting	Initially include all review disciplines (to hold time)	Any items not covered during originally scheduled time	1 hour
When PI is substantially complete, send label to applicant, OPDP and Patient Labeling Team			
8 th Meeting (Schedule 2-3 weeks after labeling sent to applicant)	Review revised labeling from applicant, include all review disciplines and OPDP and PLT		1.5 hours

¹ Based on notes from Patricia Keegan, M.D. on August 3, 2015

¹ Begin to schedule meetings two to three weeks after the mid-cycle meeting. Schedule one hour to one and one-half hour meetings depending on label section and content to be reviewed. Schedule 2 meetings weekly until all meetings are scheduled.

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/s/

IDARA UDOH
11/04/2016

Udoh, Idara

From: Udoh, Idara
Sent: Friday, October 14, 2016 4:19 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Clinical Pharmacology): BLA761049/EMD
Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Ms. Pappalardo. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application, under BLA 761049, which is currently under review.

Our clinical pharmacology reviewer has the following comments pertaining to the popPK and ER analysis:

- 1. Reference is made to Module 5.3.3.5 Population PK Study Reports in BLA 761049 Submission 0003. Please submit the analysis datasets (avelumab_PA_300616a.csv and avelumab_PA_260816a_filtered.csv), by **October 31, 2016.****
- 2. Reference is made to Module 5.3.4.2 Patient PD and PK/PD Study Reports in BLA 761049 Submission 0003. Please submit the analysis code and dataset (which contains both the exposure metrics and efficacy endpoints) for the exposure-efficacy analyses, by **October 31, 2016.****
- 3. Reference is made to Module 5.3.5.3 Integrated Exposure Safety-Exposure-Safety Analysis in BLA 761049 Submission 0003. Please submit the analysis code and dataset (which contains both the exposure metrics and safety endpoints) for the exposure-safety analyses, by **October 31, 2016.****

If you have submitted these codes and datasets, please identify the location within the current submission by **October 31, 2016.**

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
U.S. Food and Drug Administration
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/s/

IDARA UDOH
11/03/2016

Udoh, Idara

From: Udoh, Idara
Sent: Thursday, November 03, 2016 3:49 PM
To: Udoh, Idara
Subject: FW: follow-up from recent voicemail
Attachments: Acknowledge Complete BLA_BLA761049_EMD Serono.pdf

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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From: Udoh, Idara
Sent: Friday, October 14, 2016 1:41 PM
To: 'Virginia Pappalardo'
Subject: RE: follow-up from recent voicemail

Good afternoon, Virginia. I hope this message finds you well.

Attached, you will find a courtesy BLA Acknowledgement Letter, under BLA761049. It will be sent through postal mail.

Also, regarding the CRFs that were inadvertently omitted in the September 23, 2016 submission, please send as soon as possible as a BLA amendment. Refer to the September 23rd submission in your BLA amendment.

Regarding your upcoming Application Orientation Meeting, I note the following:

- 1) any slides you would like presented at Tuesday's meeting should be sent to me by COB Monday, October 17, 2016.
- 2) FDA's Office of Security Operations has cleared the following individuals for the meeting: Jacques Mascaro; Stefanie Fischer; Achta le Bourhis; Philippe Serrano; Anja von Heydebreck; Isabell Speit.

Finally, for the meeting, it has been brought to my attention that only one representative per scientific discipline (i.e. clinical, nonclinical, stats) should be present for the meeting. Since this is short notice for your group, if more than one representative will be present per discipline at this meeting, please elect a single individual per discipline to address any discipline-specific questions that may be asked.

I will be in the office today until 4p, so feel free to contact me with any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
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From: Virginia Pappalardo [<mailto:virginia.pappalardo@emdserono.com>]
Sent: Thursday, October 06, 2016 11:05 AM
To: Udoh, Idara
Subject: Re: follow-up from recent voicemail

Hi Idara
Four things I'm hoping to touch base on.

1. We haven't received the FDA acknowledgement letter for the final piece of the BLA and would appreciate this for our records. **You should be receiving it today or tomorrow.**
2. The inspection for our Vevey site is scheduled for November 7-15; we are curious whether the Aubonne site will also be inspected.
3. **During the final QC of our MAA for avelumab MCC we realized we inadvertently did not include 8 CRFs (out of nearly 600) in the BLA. These CRFs are from study 001 and were for patients in the dose escalation phase (i.e., 3mg and 20mg). We're looking for your input on how best to handle this.**
4. Could you please confirm whether we should expect questions before the AOM and/or biostatistics-dataset presentation? **No questions from FDA. This is your opportunity to present your application to us.**

Thank you in advance for your input.

Kindest regards,
Virginia

Virginia Pappalardo, RAC

Avelumab Global Regulatory Lead - MCC
Mobile: (b) (6)

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/s/

IDARA UDOH
11/03/2016

Udoh, Idara

From: Udoh, Idara
Sent: Thursday, November 03, 2016 3:46 PM
To: Udoh, Idara
Subject: RE: follow-up from recent voicemail

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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From: Udoh, Idara
Sent: Sunday, October 16, 2016 4:59 PM
To: 'Virginia Pappalardo'
Subject: RE: follow-up from recent voicemail

One last request, Virginia.

Can you confirm the following, **and** provide points of contact for each, as this information was not included with the September 23, 2016 submission (or may have been overlooked):

- 1) the location of the trial master file (unclear if it is (b) (4))
- 2) the location of the IRC Vendor for review of the data generated from this CRO.

Let me know if you have any questions or concerns.

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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/s/

IDARA UDOH
11/03/2016

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, October 18, 2016 11:51 AM
To: 'Virginia Pappalardo'
Subject: [FDA Request for Additional Information] EMD Serono/BLA 761049/Avelumab/Tx of mMCC

Good morning, Ms. Pappalardo. I hope this message finds you well.

FDA refers to your September 23, 2016, Biologics License Application (BLA), under BLA761049 for Bavencio. We also refer to our October 16, 2016 information request for you to provide the locations of 1) the trial master file for study EMR 100070-003 entitled "A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab (MSB0010718C) in subjects with Merkel cell carcinoma", and 2) the IRC vendor. We acknowledge receipt of your response to the October 16, 2016 information request, received on October 17, 2016.

It remains unclear whether (b) (4) maintains the **complete trial master file (TMF)** at its (b) (4) location or if there are parts of the TMF that are retained by EMD Serono due to its proprietary nature. For inspection purposes, please confirm whether the complete TMF is with (b) (4); and if not, what components of the TMF are maintained by EMD Serono and the location.

Your response is requested via email, in addition to a formal submission to your IND as soon as possible. Please acknowledge receipt of this e-mail and feel free to contact me if you have any questions.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER
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/s/

IDARA UDOH
11/03/2016

Udoh, Idara

From: Udoh, Idara
Sent: Thursday, October 20, 2016 8:55 AM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (Pharmacovigilance): BLA761049/EMD
Serono/Bavencio/Treatment of Merkel Cell Carcinoma
Attachments: FDA Guidance.Good PV Practices and PE Assessment.2005.pdf; FDA Guidance.E2E PV Planning.2005.pdf

Good morning, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application (BLA), under BLA 761049, which is currently under review.

FDA encourages sponsors to submit a Pharmacovigilance Plan designed to detect new safety risks and to further evaluate identified safety risks with **avelumab** following market approval. Guidance for pharmacovigilance planning is included in the FDA Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (2005), and the FDA Guidance for Industry on E2E Pharmacovigilance Planning (2005). If the plan is available, please include it in the BLA application in the appropriate module so it can be reviewed accordingly.

We respectfully request your response **no later than October 31, 2016**, via email in addition to a formal submission to your BLA. Please acknowledge receipt of this e-mail and feel free to contact me if you have any questions.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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IDARA UDOH
11/03/2016

Udoh, Idara

From: Udoh, Idara
Sent: Tuesday, October 18, 2016 4:10 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request (QT IRT): BLA761049/EMD Serono/Bavencio/Treatment of Merkel Cell Carcinoma

Good afternoon, Virginia. I hope this message finds you well.

FDA refers to your September 23, 2016 Biologics Licensing Application (BLA), under BLA 761049, which is currently under review.

Our QT Interdisciplinary Review Team has the following comments and requests submission of items for Integrated ECG and Exposure-QTc analysis:

- (1) Correction factor (beta) of QTcP
- (2) Only small portions of ECGs were uploaded to ECG Warehouse—1183 out of 18000s—for Study EMR100070-001, please submit the rest of them. If no digital format is available, please submit them in PDF to FDA directly. Same for Study EMR100070-002 and EMR100070-003.
- (3) Please submit pooled analysis dataset (3 studies) and program codes. The PK/PD analysis dataset combines ECG intervals, their baseline, delta with drug concentration, etc.

Your response is requested via email, in addition to a formal submission to your BLA as soon as possible. Please acknowledge receipt of this e-mail and feel free to contact me if you have any questions.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2
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IDARA UDOH
11/03/2016

Udoh, Idara

From: Udoh, Idara
Sent: Friday, September 23, 2016 3:27 PM
To: 'Virginia Pappalardo'
Subject: FDA Information Request: BLA 761049/EMD Serono, Inc./Avelumab/Tx of metastatic Merkel cell carcinoma

Good afternoon, Virginia. I hope this message finds you well.

On August 29, 2016, FDA received notification that study EMR100070-001 had been imported to our ECG warehouse, and that it included 1183 ECGs from 209 subjects. It seems that the study report has not been submitted to the BLA. Can you confirm whether it would be included as part of the submission coming in today? If not, please forward Study EMR100070-001 as soon as possible and submit the following as it relates to Study EMR100070-001:

- a. *Annotated CRF*
- b. *A data definition file which describes the contents of the electronic data sets*
- c. *Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses*
- d. *Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g, QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable)*
- e. *Data set whose QT/QTc values are the average of the above replicates at each nominal time point*
- f. *Narrative summaries and case report forms for any*
 - i. *Deaths*
 - ii. *Serious adverse events*
 - iii. *Episodes of ventricular tachycardia or fibrillation*
 - iv. *Episodes of syncope*
 - v. *Episodes of seizure*
 - vi. *Adverse events resulting in the subject discontinuing from the study*
- g. *A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (attached)*

Let me know if you have any questions or concerns.

Best,

Idara Udoh, MS
Senior Regulatory Health Project Manager
Division of Oncology Products 2

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/s/

IDARA UDOH
11/03/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761049

INFORMATION REQUEST

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Ms. Pappalardo:

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

We also refer to your 23 September 2016 submission, containing the rolling Biologics License Application (BLA) seeking approval for avelumab, a fully human immunoglobulin (Ig) G1 monoclonal antibody directed against PD-L1.

We are reviewing the CMC sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your BLA by **04 November 2016**.

We have the following CMC IR:

1. Labeling

Avelumab drug product does not contain a preservative. The proposed labeling claims that drug product diluted in 0.9% or 0.45% sodium chloride solution may be stored refrigerated at 2-8°C (36-46°F) (b) (4) for up to 24 hours. Please submit microbiological studies to support the 24 hour storage time at 2- 8°C (b) (4)

(b) (4). Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions for twice the recommended storage period, and use the label-recommended diluent. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-dilution storage period is not more than 4 hours at 2-8°C or at room temperature.

2. Container closure integrity test Microbial immersion:

- a. Please clarify and confirm if the vials used for qualification of microbial immersion CCI test methods are the same as the commercial vials described in 3.2.P.7.
- b. The microbial immersion CCI test method was not qualified using worst case pressure or vacuum challenge and a compromised positive control. Compromised positive-control vials with known breach sizes should be included and exposed to the same worst case conditions as the test vials to assess the efficiency of the CCI test method.

Capping Force

- c. Please provide CCI test results obtained using with worst-case crimping process parameters to qualify the container closure system for avelumab drug product.

3. Manufacturer(s)

It is not clear whether all drug product QC, lot release and stability tests are performed at each site where QC, lot release and stability testing is specified in 3.2.P.3.1. Update the BLA with the specific tests that are being performed at each of the sites.

4. Drug product manufacturing process

(b) (4)

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by 04 November 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, please contact me, at (240) 402-5826 or at truong.quach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Truong
Quach -S

Digitally signed by Truong Quach
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Truong Quach -S,
0.9.2342.19200300.100.1.1=20015
11949
Date: 2016.11.02 15:06:18 -04'00'

Truong Quach, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



BLA 761049

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

EMD Serono, Inc.
45A Middlesex Turnpike
Billerica, MA 01821

ATTENTION: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs

Dear Ms. Pappalardo:

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

We also refer to your correspondence, dated and received August 22, 2016, requesting review of your proposed proprietary name, Bavencio.

We have completed our review of the proposed proprietary name, Bavencio and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your August 22, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-4901. For any other information regarding this application, contact Idara Udoh, Regulatory Project Manager in the Office of New Drugs at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
10/28/2016



BLA 761049

BLA ACKNOWLEDGMENT

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

Dear Ms. Pappalardo:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Bavencio (avelumab) Injection, for intravenous use, 20 mg/mL

Date of Application: September 23, 2016

Date of Receipt: September 23, 2016

Our Reference Number: BLA 761049

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 22, 2016, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit 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>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MELANIE B PIERCE
10/14/2016



BLA 761049

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

EMD Serono, Inc.
45A Middlesex Turnpike
Billerica, MA 01821

ATTENTION: Virginia Pappalardo, RAC
Associate Director, Global Regulatory Affairs

Dear Dr. Pappalardo:

Please refer to your Biologics License Application (BLA) dated and received September 23, 2016, submitted under section 351(a) of the Public Health Service Act for Avelumab, 10 mg/kg.

We acknowledge receipt of your correspondence, dated and received August 22, 2016, requesting a review of your proposed proprietary name, Bavencio.

If the application is filed, the user fee goal date will be November 20, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Idara Udoh, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Latonia Ford, RN, BSN, MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LATONIA M FORD
10/12/2016



BLA 761049

ACKNOWLEDGE PRESUBMISSION

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

Dear Ms. Pappalardo:

We have received the first section of your Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act for the following:

Name of Drug Product:	Bavencio (avelumab) Injection, for intravenous use 20 mg/mL
Date of Submission:	September 2, 2016
Date of Receipt:	September 2, 2016
Our Reference Number:	BLA 761049

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite BLA 761049 listed above at the top of the first page of any communications concerning this application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to

set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

IDARA UDOH
09/14/2016



IND119394

MEETING MINUTES

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avelumab.

We also refer to the teleconference between representatives of your firm and the FDA on September 2, 2016. The purpose of the meeting was to discuss recent scientific advice received from the EMA Scientific Advice Working Party (SAWP) regarding your proposed study EMR 100070-006, entitled "A Phase III multicenter study of avelumab (MSB0010718C) versus chemotherapy in systemic chemotherapy treatment naïve patients with metastatic Merkel cell carcinoma," to verify the clinical benefit of avelumab for the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

APPEARS THIS WAY ON ORIGINAL

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance

Meeting Date and Time: September 2, 2016; 11:00 AM – 12:00 PM, EST
Meeting Location: N/A (Teleconference)

Application Number: IND 119394
Product Name: avelumab
Indication: Metastatic Merkel cell carcinoma (mMCC) in patients with disease progression after at least one previous chemotherapy regimen
Sponsor/Applicant Name: EMD Serono, Inc.

Meeting Chair: Suzanne Demko
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Center for Drug Evaluation and Research, Division of Oncology Products 2 (DOP 2)

Patricia Keegan, Director
Suzanne Demko, Clinical Team Leader
Denise Casey, Clinical Reviewer
Martha Donoghue, Acting Associate Director
Missiratch Biable, Acting Team Lead, Project Management Staff
Idara Udoh, Senior Regulatory Health Project Manager

EMD SERONO, INC./ PFIZER ATTENDEES

Murtuza Bharmal, Director, Global Evidence & Value Development
Kevin Chin, Executive Medical Director, Immuno-Oncology, Global Research and Early Development, EMD Serono, Inc.
Vijay Kasturi, Medical Director, Oncology Medical Affairs
Alex Kuta, Vice President, R&D Global Regulatory Affairs
Lisa Mahnke, MCC Medical Lead, Global Research and Early Development, EMD Serono, Inc.
Jacques Mascaro, Senior Vice President, Head of Global Regulatory Affairs and R&D Quality
Alina Micu, Principal Clinical Operations Lead
Virginia Pappalardo, Global Regulatory Lead, Global Regulatory Affairs, EMD Serono, Inc.
Philippe Serrano, Global Head, Regulatory Affairs Oncology, Merck KGaA
Jennifer Stevens, Global Regulatory Affairs Program Lead, EMD Serono, Inc.
Anja Von Heydebreck, Global Biostatistics, Merck KGaA
Reinhard von Roemeling, Senior Vice President, Clinical
Laurie Strawn, Global Regulatory Portfolio Lead, Pfizer

MEETING PURPOSE

On July 5, 2016, EMD Serono, Inc. (“EMD Serono”) requested a Type B meeting to discuss with FDA the recent scientific advice received from the EMA Scientific Advice Working Party (SAWP) regarding their proposed confirmatory study EMR 100070-006 (Study 006), entitled “A Phase III multicenter study of avelumab (MSB0010718C) versus chemotherapy in systemic chemotherapy treatment naïve patients with metastatic Merkel cell carcinoma,” to verify the clinical benefit of avelumab for the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen.

EMD Serono is planning to submit a BLA under the provisions of 21 CFR 601 subpart E based on the results of Protocol EMR100070-003, entitled “A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects with Merkel Cell Carcinoma”. On July 6, 2016, FDA received Part 1 of EMD Serono’s BLA, and it is expected that the confirmatory study (Study 006) will be ongoing at the time of the complete BLA submission.

The meeting briefing package for this meeting was received on July 5, 2016.

FDA sent Preliminary Comments to EMD Serono on August 10, 2016.

PROPOSED INDICATION

For the treatment of patients with mMCC with disease progression after at least one previous chemotherapy regimen.

BACKGROUND

On June 16, 2016, a pre-BLA meeting was held to discuss EMD Serono’s plans to seek accelerated approval for avelumab and to reach agreement on the content and format of the BLA. During the meeting, EMD Serono summarized the challenges it has encountered in designing a feasible, randomized controlled confirmatory trial and the advice provided by EMA regarding potential study designs required based on conditional approval for avelumab in Europe. FDA requested that EMD Serono submit a meeting request to discuss the latest proposal for a confirmatory study and to provide additional information regarding the global development program for avelumab in mMCC.

Clinical Development Program in mMCC

Study EMR 100070-00(Study 003) Part A

EMD Serono plans to use the data from Study 003 to support the original BLA for avelumab seeking approval under the provisions of 21 CFR 601 Subpart E. Part A of the trial is an ongoing, multicenter, open label, single arm study of avelumab in 88 patients with mMCC who

have progressed following at least one previous course of chemotherapy. The primary endpoint is confirmed objective response rate (ORR) according to RECIST 1.1., as determined by an independent review committee (IRC), in the modified intent-to-treat (mITT) population (any patient who received at least one dose of avelumab). The key eligibility criteria for the population supporting the request for accelerated approval are adult patients with histologically proven mMCC who received at least one acceptable line of prior chemotherapy for their metastatic disease, and disease progression after the most recent line of chemotherapy. The acceptable lines of prior chemotherapy included carboplatin, cisplatin, and etoposide in combination with carboplatin or cisplatin, cyclophosphamide, topotecan, doxorubicin, epirubicin, or vincristine. Patients were required to have measurable disease (according to RECIST 1.1) including skin lesions, an ECOG Performance Status of 0 to 1, and a life expectancy of more than 12 weeks. Treatment consists of avelumab at a dose of 10 mg/kg administered via IV infusion once every 2 weeks administered until intolerable toxicity or significant clinical deterioration, regardless of radiologic disease progression.

Based on agreement with FDA during the conduct of the study, the data cutoff date for the primary analysis (six months after start of avelumab in the last patient enrolled) is March 3, 2016; a supportive analysis to further characterize durability of response is planned when the last patient had been followed for 12 months since initiation of avelumab. There are 88 patients in the mITT population with a median follow-up time of 10 months (range 6 to 19 months). According to the briefing document provided in preparation for the pre-BLA meeting, the ORR is 32% (95% CI: 22, 43), consisting of eight complete responses and 20 partial responses. The median duration of response (DOR) was not estimable; however, 26 responding patients (92%) had responses durable for at least 6 months.

Study 003 Part B

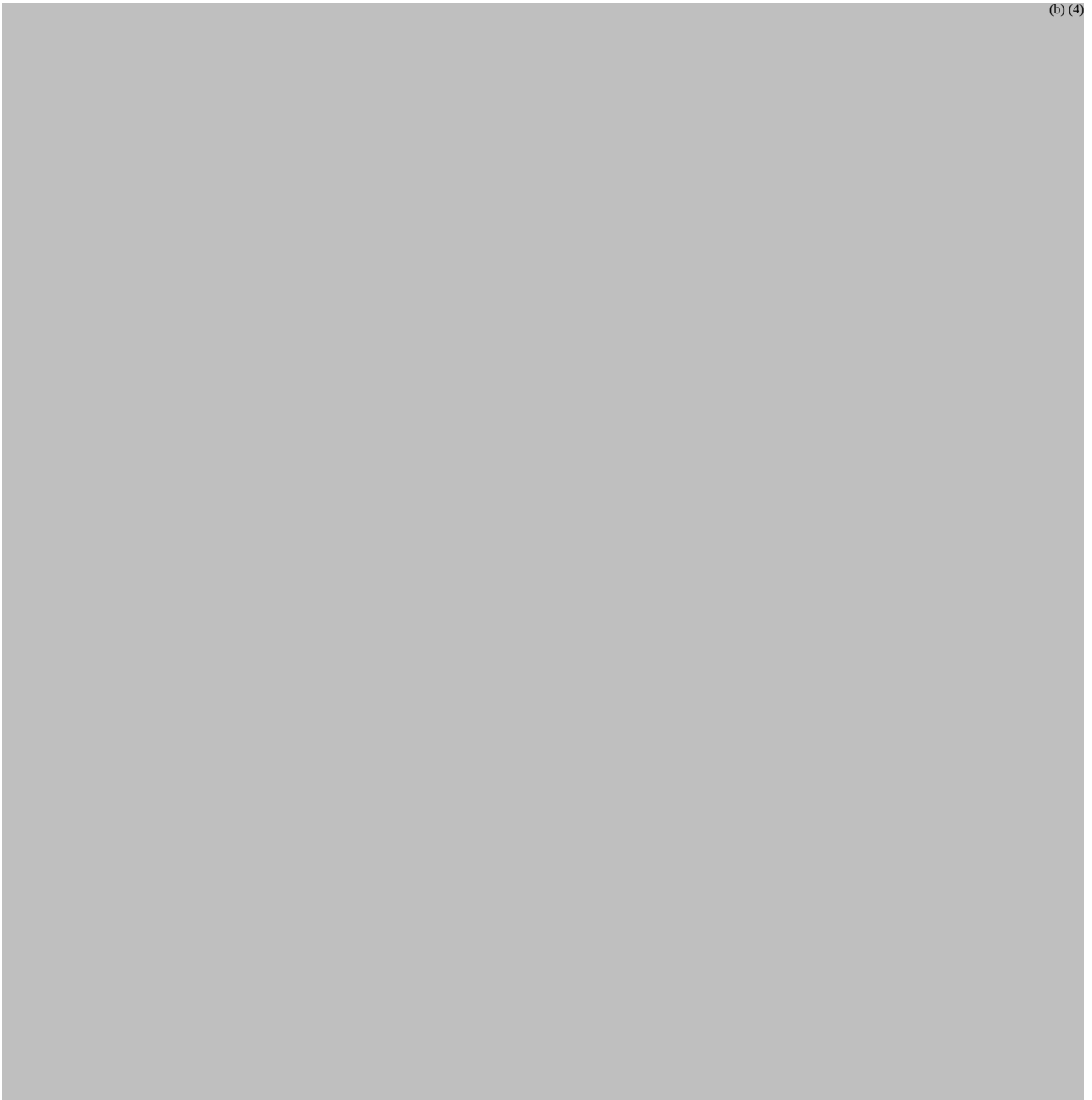
EMD Serono submitted a revised Protocol 003 (reference IND 119394, SN 0225 submitted March 24, 2016; and subsequent amendment SN 0239 submitted April 15, 2016) to incorporate a new cohort (Part B) of 50 patients with metastatic or distally recurrent MCC who have not received treatment for metastatic disease. The study population is defined as having Stage IV disease, and being treatment-naïve in the metastatic setting. Prior adjuvant chemotherapy is allowed if the end of treatment is greater than six months prior to entry. Patients with baseline immunodeficiency are excluded. The primary endpoint is six month durable response rate (DRR), defined as the proportion of patients with an objective response of at least six months in duration. The responses must be confirmed as per RECIST 1.1 and will be assessed by an IRC. The study aims to demonstrate a DRR greater than 18%. According to the briefing document, the proposed sample size of 50 patients will provide 90% power to reject the null hypothesis of a $DRR \leq 18\%$ at a one-sided level of 0.025 using the exact binomial test, given an assumed true DRR of 40% with avelumab treatment.

Study EMR100070-006 (Study 006)

Study 006 is the planned trial intended to demonstrate confirmatory evidence of the clinical benefit of avelumab for patients with mMCC. Multiple study designs for Protocol 006 have been

proposed by EMD Serono and reviewed and discussed with FDA. Summarized, they are as follows:

(b) (4)



Observational Study 100070-Obs001 (Obs001)

Study Obs001 is a multicenter, retrospective observational study conducted by EMD Serono to assess clinical outcomes of patients with mMCC following treatment with chemotherapy. The objective of this study is to evaluate the natural history of a patient population similar to those enrolling in Study 003 (i.e., patients with chemotherapy refractory mMCC) with regard to ORR, DOR, PFS and overall survival (OS). The study was amended in January 2016 to additionally

assess treatment outcomes for patients receiving frontline chemotherapy. EMD Serono proposes to use the data generated from Study Obs001 to serve as an adequate historical control for chemotherapy effectiveness in frontline and refractory mMCC. EMD Serono states that the results from the observational study are consistent with a published retrospective analysis of treatment outcomes conducted in a US cohort of 62 patients with mMCC [Iyer et al., *Cancer Med*]. The briefing document provides a side-by-side overview of results from Study 003, Study Obs001 and the Iyer retrospective analysis (Table 4 copied from briefing document):

Table 4: Results of EMR100070-003 and Observational Study (Study 100070-Obs001) (not intended as a formal statistical comparison)

Efficacy Parameter	EMR100070-003 N=88 N (%) 2L+	Observational Study Part A (US)* N=20 N (%) 2L+	Observational Study Part B (EU)* N=34 N (%) 2L+	Observational Study Part A (US)* N=67 N (%) 1L	Historical Literature (US) Iyer et al. N=30 % 2L	Historical Literature (US) Iyer et al. N=62 % 1L
BOR per RECIST v1.1			BOR per physician clinical judgement			
Complete Response	8 (9.1)	0	0	10 (14.9)	1 (3.3)	8 (13)
Partial Response	20 (22.7)	4 (20.0)	3 (8.8)	11 (16.4)	6 (20.0)	26 (42)
Stable Disease	9 (10.2)	2 (10.0)	3 (8.8)	1 (1.5)	1 (3.3)	4 (6)
Progressive Disease	32 (36.4)	8 (40.0)	28 (82.4)	31 (46.3)	22 (73.3)	24 (39)
Non-CR /Non-PD	1 (1.1)	0	0	0	0	0
Not Evaluable	18 (20.5)	6 (30.0)	0	14 (20.9)	0	0
Objective Response Rate						
Response rate, CR+PR (95% CI)	28 (31.8) (21.9, 43.1) ^a	4 (20.0) (5.7, 43.7)	3 (8.8) (1.9, 23.7)	21 (31.3) (20.6, 43.8)	7 (23.3) (9.9, 42.3)	55
Sensitivity Analysis, ORR (measurable disease plus available on-treatment assessments) Response rate, CR+PR (95% CI)	N=64 26 (40.6) (28.5, 53.6)				23.3	
Duration of Response						
Median, months (95% CI)	NE (8.3, -)	1.7 (0.5, 3.0)	1.9 (1.3, 2.1)	5.7 (2.6, 8.7)	4.2	2.8
≥ 6 months by K-M, % (95% CI)	92 (70, 98)	0	0		-	-
Durable response rate at 6 months, %, 95% CI	29.1 (19.5, 38.8)	0 (0.0, 16.8)	0 (0.0, 10.3)	14.9 (7.4, 25.7)	6.7 (0.8, 22.1)	17.7 (9.2, 29.5)

Discussions with EMA regarding confirmatory trial design

(b) (4)

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing

application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

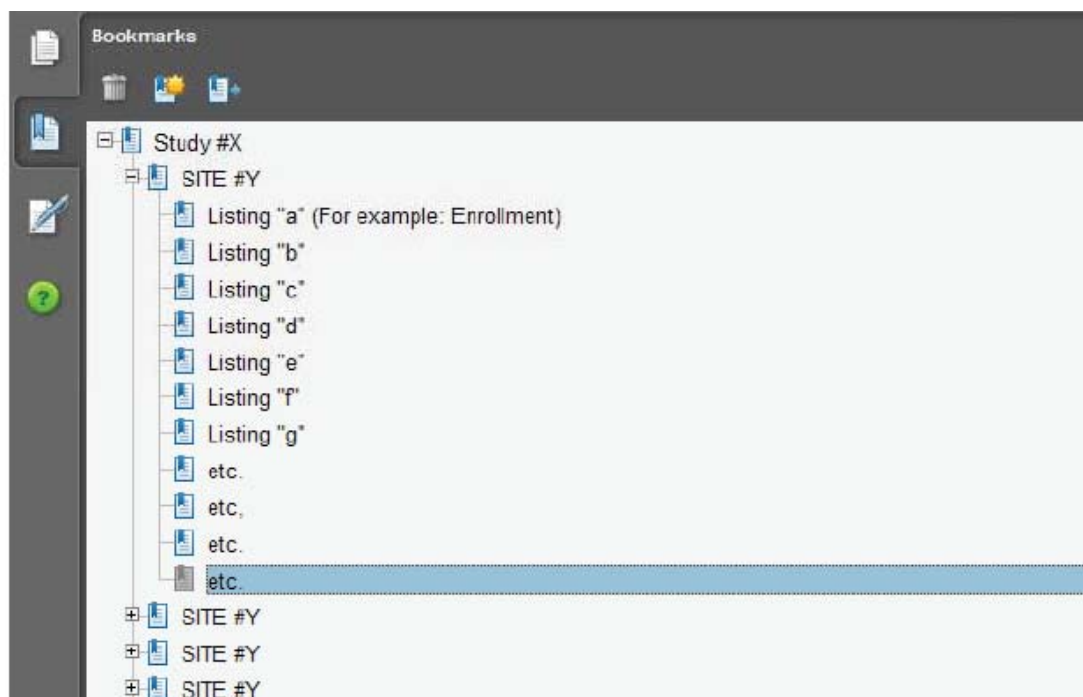
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is

- the actual physical site(s) where documents are maintained and would be available for inspection
- b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

No attachments and handouts.

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

/s/

IDARA UDOH
09/07/2016



BLA 761049/0

ACKNOWLEDGE PRESUBMISSION

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

Dear Ms. Pappalardo:

We have received the first section of your Biologics License Application (BLA) under the program for step-wise submission of sections of a marketing application under 351 of the Public Health Service Act for the following:

Name of Drug Product:	Bavencio (avelumab) Injection, for intravenous use 20 mg/mL
Date of Submission:	July 6, 2016
Date of Receipt:	July 6, 2016
Our Reference Number:	BLA 761049/0

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite BLA 761049/0 listed above at the top of the first page of any communications concerning this application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to

set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

IDARA UDOH
07/18/2016



IND119394

**MEETING MINUTES
GRANT ROLLING REVIEW**

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avelumab.

We also refer to the meeting between representatives of your firm and the FDA on June 16, 2016. The purpose of the meeting was to discuss and reach agreement on the content and format of your Biologic License Application (BLA) for avelumab for the proposed indication of the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA/Breakthrough Therapy

Meeting Date and Time: June 16, 2016; 11:00 AM – 12:00 PM, EST
Meeting Location: White Oak Building 22, Conference Room 1421

Application Number: IND 119394
Product Name: Avelumab (MSB0010718C)
Indication: Metastatic Merkel cell carcinoma (mMCC) in patients with disease progression after at least one previous chemotherapy regimen
Sponsor/Applicant Name: EMD Serono, Inc.

Meeting Chair: Suzanne Demko
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Center for Drug Evaluation and Research, Division of Oncology Products 2 (DOP 2)

Patricia Keegan, Director
Suzanne Demko, Clinical Team Leader
Kaushikkumar Shastri, Clinical Reviewer
Denise Casey, Clinical Reviewer
Melanie Pierce, Chief, Project Management Staff
Idara Udoh, Senior Regulatory Health Project Manager
Anuja Patel, Senior Regulatory Health Project Manager

Center for Drug Evaluation and Research, Division of Hematology Oncology and Toxicology (DHOT)

Whitney Helms, Nonclinical Team Leader
Alexander Putman, Nonclinical Reviewer

Center for Drug Evaluation and Research, Office of Clinical Pharmacology

Hong Zhao, Clinical Pharmacology Team Leader
Ruby Leong, Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biometrics V (DBV)

Kun He, Statistical Team Leader
Xiaoping Jiang, Statistical Reviewer

Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research II (DBRR-II)

Chris Downey, Product Quality Team Leader
Arulvathani Arudchandran, Product Quality Reviewer

EASTERN RESEARCH GROUP (ERG) ATTENDEES

Christopher Sese, ERG Assessor

SPONSOR ATTENDEES

EMD Serono, Inc.

Kevin Chin, Executive Medical Director, Immuno-Oncology, Global Research and Early Development
Jean-Marie Cuillerot, Global Head, Early Clinical Development Immuno-Oncology
Haiqing (Isaac) Dai, Director, Clinical Pharmacology
Pascal Girard, Director, Pharmacometry
Alex Kuta, Head, US Regulatory Affairs
Lisa Mahnke, Medical Lead
Virginia Pappalardo, Global Regulatory Lead, Global Regulatory Affairs
Alise Reicin, Senior Vice President, Head of Global Clinical Development
Byron Robinson, Senior Vice President and Program Team Leader, Immunooncology
Jennifer Stevens, Global Regulatory Affairs Program Lead

Merck KGaA

Gülderen Güzel, Global Drug Safety
Jacques Mascaro, Senior Vice President, Head of Global Regulatory Affairs and R&D Quality
Philippe Serrano, Global Head, Global Regulatory Affairs
Isabell Speit, Global Drug Safety
Anja Von Heydebreck, Global Biostatistics

Pfizer

Philip Witman, Global Regulatory Lead
Laurie Strawn, Global Regulatory

MEETING PURPOSE

On April 20, 2016, EMD Serono, Inc. (“EMD Serono”) requested a Type B pre-BLA meeting to discuss and reach agreement on the content and format of their planned Biologic License Application (BLA) for avelumab for the proposed indication of the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen, and to discuss and reach agreement on the design of the trial intended to confirm clinical benefit.

EMD Serono is planning to submit a BLA under the provisions of 21 CFR 601 subpart E based on the results of Protocol EMR100070-003, entitled “A Phase II, Open-Label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects with

Merkel Cell Carcinoma”. It is expected that the confirmatory study (Protocol EMR100070-006) will be ongoing at the time of the BLA submission.

The meeting briefing package for this meeting was received on May 17, 2016.

PROPOSED INDICATION

For the treatment of patients with mMCC who have disease progression after at least one previous chemotherapy regimen.

BACKGROUND

Regulatory History

On November 13, 2013, IND 115747 was submitted to the Division of Oncology Products 2 for avelumab for the treatment of patients with various solid tumors. The IND was placed on partial hold on December 12, 2012 for insufficient information provided in the IND to assess whether the safety testing in the master cell bank (MCB) was sufficient to exclude contamination by (b) (4) [REDACTED] adventitious agent. The initial feasibility study was allowed to proceed; however, EMD Serono was required to provide data demonstrating that the MCB was free of adventitious agents (b) (4) [REDACTED]. This information was submitted on July 3, 2013, and the partial hold was removed on August 1, 2013.

On January 14, 2014, a pre-IND teleconference was held between FDA and EMD Serono to discuss their proposed development program for the treatment of MCC and the design of Protocol EMR 100070-003, entitled, “A Phase 2, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of MSB0010718C in Subjects with Merkel Cell Carcinoma (MCC).” The study is (b) (4) [REDACTED]

[REDACTED] EMD Serono agreed to narrow the study population to patients with mMCC who have progressed after they have received

chemotherapy for the treatment of a metastatic disease or who are not suitable candidates for chemotherapy because of underlying medical conditions.

- [REDACTED] (b) (4)
[REDACTED] EMD
Serono should provide justification for the proposed effect size and duration of effect as either evidence of direct benefit or likely to predict clinical benefit based on a lower limit of the confidence interval observed around the response rate. [REDACTED] (b) (4)
[REDACTED]
- FDA requested that EMD Serono submit a proposal for a confirmatory study evaluating time-to-event endpoints for FDA review prior to initiating the study.

On March 4, 2014, the development program of avelumab in mMCC was submitted under IND 119394; the program would rely on Protocol EMR 100070-003 (Study 003), a single-arm, multicenter study in 88 patients with mMCC who had received at least one line of previous chemotherapy to support a request for accelerated approval. The primary endpoint of Study 003 is BOR, according to RECIST 1.1 based on independent review, with the aim of demonstrating that the estimated BOR was greater than 20% by the exact binomial test.

A Type B CMC meeting was held on December 14, 2014 to discuss the scale-up activities and comparability for Process B drug substance. Process B material is intended for phase 3 development and is the intended commercial drug substance manufacturing process. Data supporting the comparability was submitted to the IND on March 10, 2015 and deemed sufficient for introduction into clinical trials.

On June 12, 2015, a Breakthrough Therapy Designation (BTD) preliminary advice request was submitted to FDA to discuss whether a request for BTD for avelumab in patients with mMCC was appropriate based on the data derived from the pre-specified futility analysis (n= 20 patients) performed during Study 003. A teleconference was held on July 1, 2015, and FDA recommended additional data on more patients with longer follow-up be included in any formal BTD request. FDA specifically recommended that the BTD request be submitted when EMD Serono had a minimum of three months, but preferably six months, of follow-up data on responders.

On August 25, 2015, EMD Serono submitted a draft protocol for Study EMR 100070-006 (Study 006), intended to provide confirmatory evidence of clinical benefit in patients with mMCC such that a potential indication for mMCC approved under accelerated approval could receive regular approval. [REDACTED] (b) (4)
[REDACTED]

(b) (4)

On September 18, 2015, EMD Serono submitted a BTB request for avelumab for the treatment of patients with mMCC that have progressed after at least one previous chemotherapy regimen. Breakthrough Therapy Designation for this indication was granted on November 17, 2015.

On September 21, 2015, avelumab was granted orphan drug designation for the treatment of MCC.

On October 1, 2015, Fast Track Designation was granted to EMD Serono for the development of avelumab for the treatment of patients with mMCC to demonstrate a clinically important and statistically robust improvement in PFS for patients treated with avelumab compared to available therapy.

On February 2, 2016, an Initial Comprehensive Multidisciplinary Breakthrough Therapy meeting was held to discuss EMD Serono's plans to seek accelerated approval for avelumab and to reach agreement on Study 006.

On February 5, 2016, EMD Serono submitted a request for proprietary name review of Bavencio. FDA determined that Bavencio was conditionally acceptable on April 28, 2016.

Separate discipline-specific pre-BLA meetings were granted to discuss the adequacy of EMD Serono's clinical pharmacology; chemistry, manufacturing, and controls (CMC); and nonclinical toxicology programs to support the planned BLA for avelumab. FDA issued Meeting Minutes on April 18, 2016, May 24, 2016, and June 8, 2016, respectively.

FDA sent Preliminary Comments to EMD Serono on June 15, 2016.

APPEARS THIS WAY ON ORIGINAL

Chemistry, Manufacturing, and Controls (CMC)

Avelumab (MSB0010718C, an anti-PD-L1 human IgG1 λ mAb) drug product is a concentrated solution for intravenous use. MSB0010718C binds PD-L1 and blocks its interaction with programmed death-1 receptor (PD1). The intended commercial presentation contains 20-mg/mL of avelumab in type 1 glass vials with the filled volume of (b) (4) ml. The proposed long-term storage for drug product is at $5 \pm 3^{\circ}\text{C}$.

The avelumab drug substance is (b) (4). The drug substance is manufactured from (b) (4) at Merck Serono in Vevey, Switzerland. The initial clinical trial and the ongoing Study 003 utilizes drug product derived from the Process A drug substance manufactured at (b) (4). This drug product was manufactured at Aubonne, Switzerland. Process B material was introduced in Study EMR 100070-001 in April 2015 and was the material used in (b) (4). Process B drug substance differs from Process A by (b) (4). Materials from both processes are considered physicochemically comparable by the sponsor and the sponsor will seek approval of the Process B material.

During the pre-BLA CMC meeting held on April 26, 2016, FDA agreed with EMD Serono's proposal for the content of the planned BLA and plans to schedule a manufacturing campaign during November 2016 to facilitate a pre-license inspection.

Nonclinical

To support the BLA filing, EMD Serono conducted nonclinical studies to assess in vitro and in vivo pharmacology, pharmacokinetics, cytokine release, tissue cross-reactivity, and phototoxicity. A Good Laboratory Practice (GLP)-compliant repeated-dose toxicity study was conducted in cynomolgus monkeys for 13 weeks with an 8-week recovery period. Genotoxicity and reproductive toxicity studies will not be conducted.

As communicated in the pre-BLA nonclinical Written Responses Only meeting issued on June 8, 2016, the proposed nonclinical package described in the pre-meeting materials appeared adequate to support filing of the BLA; however, the acceptability of data from nonclinical studies will be determined during review of all data included in the original BLA. FDA reminded EMD Serono that while an embryofetal development study in non-human primates does not appear warranted, potential reproductive and development effects will need to be included in any marketing application. FDA also recommended including any available data on the potential effects of avelumab on the immunologic recall or memory response.

Clinical

Study EMR 100070-003(Study 003)

Study 003 is an ongoing, multicenter, open label, single arm study of avelumab in 88 patients with mMCC who have progressed following at least one previous course of chemotherapy. EMD Serono submitted a revised Protocol 003 (reference IND 119394, SN 0225 submitted March 24, 2016; and subsequent amendment SN 0239 submitted April 15, 2016) to incorporate a new cohort of 50 patients with metastatic or distally recurrent MCC who have not received treatment for metastatic disease.

The primary endpoint for Study 003 is confirmed ORR according to RECIST 1.1., as determined by an independent review committee (IRC), in the modified intent-to-treat (ITT) population (any patient who received at least one dose of study drug). The key eligibility criteria for the population supporting the request for accelerated approval are adult patients with histologically proven mMCC who received at least one acceptable line of chemotherapy for their metastatic disease, and have progressed after the most recent line of chemotherapy. The acceptable lines of prior chemotherapy included carboplatin, cisplatin, and etoposide in combination with carboplatin or cisplatin, cyclophosphamide, topotecan, doxorubicin, epirubicin, or vincristine. Patients are required to have measurable disease (according to RECIST 1.1) including skin lesions, an ECOG Performance Status of 0 to 1, and a life expectancy of more than 12 weeks. Treatment consists of avelumab at a dose of 10 mg/kg administered via IV infusion once every 2 weeks administered until intolerable toxicity of significant clinical deterioration, regardless of radiologic disease progression.

Efficacy Results

The data cutoff date for the primary analysis (6 months after start of treatment of the last patient) is March 3, 2016. There are 88 patients (65 males) in the ITT population. Patients received a median of seven doses of avelumab (range 1 to 35 doses), and the median duration of treatment was 17 weeks (range 2 to 76 weeks). Patients had a median follow-up time of 10 months (range 6 to 19 months) from first trial treatment to the analysis cut-off date. The response data are summarized by EMD Serono in the following table from the briefing package:

APPEARS THIS WAY ON ORIGINAL

Table 7: Confirmed Best Overall Response according to IRC (ITT)

Efficacy Parameter	N (%) (N=88)
Confirmed BOR per RECIST v1.1, IRC	
Complete Response	8 (9.1)
Partial Response	20 (22.7)
Stable Disease	9 (10.2)
Non-CR /Non-PD ^a	1 (1.1)
Progressive Disease	32 (36.4)
Not Evaluable ^b	18 (20.5)
Objective Response Rate	
Response Rate, CR+PR (95.9% CI ^c)	28 (31.8) (21.9, 43.1)
Duration of Response	
Median, months (95% CI)	NE (8.3, -)
Min, max	2.8, 17.5+
≥ 6 months by K-M, % (95% CI)	92 (70 , 98)
Durable response rate at 6 months, % (95% CI) ^d	29.1 (19.5, 38.8)

^a This patient did not have measureable disease at baseline and thus a best overall response of partial response or stable could not be distinguished

^b Patients non-evaluable for a confirmed best overall response had either no baseline lesions identified by the IRC (n=4), baseline but no post-baseline assessments (n=10: 4 patients who died within six weeks after start of treatment, and 6 additional patients who discontinued study treatment in the first six weeks), all post-baseline assessments that were non-evaluable (n=2), no post-baseline tumor assessment prior to start of new anticancer therapy (n=1), or stable disease of insufficient duration (< 6 weeks after start date without further evaluable tumor assessment; n=1).

^c Accounting for group sequential testing strategy.

^d Based on the ORR and the KM estimate for 6-mo durability.

BOR: Best Overall Response; CI: Confidence interval; CR: Complete response; IRC: Independent Review Committee; K-M: Kaplan-Meier; NE: Not estimable; PD: Progressive disease; PR: Partial response; RECIST: Response Evaluation Criteria in Solid Tumors version 1.1.

Avelumab Safety Profile

As of November 5, 2015, EMD Serono states that 1300 patients with various cancers in the ongoing dose-finding with expansion study (Study 001) received at least one infusion of avelumab for the treatment of patients with MCC at the proposed dose of 10 mg/kg intravenous every two weeks. The median duration of exposure was 11.5 weeks (range 2-105 weeks), including the 88 patients with mMCC enrolled in Study 003. The median duration of exposure in Study 003 was 15 weeks (range 2- 60 weeks).

As of March 3, 2016, a total of 43 (48.9%) patient deaths were reported in Study 003. Of the 43 patients who died, 12 died within 30 days after the last dose of treatment. Of these, 11 deaths were assessed by the reporting investigator as due to disease progression and not related to study drug, and one death was reported with the primary reason unknown at the time of analysis.

The following table from the briefing package shows treatment-related deaths in Study 001:

Table 13: Treatment-Related Deaths and the Events Leading to Deaths during Treatment Expansion in Trial EMR 100070-001

Subject ID/Mfr. Ctl No.	Age/Gender/Diagnosis	Avelumab Dose /Time on trial	Cause of Death
172-0004/7285199 ^a	71/F/NSCLC	10 mg/kg/ 10 days	Primary reason of death: Pneumonitis radiation induced and dyspnea (<i>downgraded to Grade 3 after data cut-off date</i>)
120-0014/7305891	51/F/MBC	10 mg/kg/ 46 days	Primary reason of death: Acute liver failure associated with autoimmune hepatitis (Grade 3) No biopsy/autopsy performed
102-0020/7265021	61/F/MBC	10 mg/kg/26 days	Fatal anoxic brain injury (not related) after cardiac arrest (related)
908-0003/7318782	50/F/GC	10 mg/kg/12 days	Primary reason of death: Autoimmune hepatitis (Grade 3) with hepatic failure and fatigue No biopsy/autopsy performed
139-0004/7319455 ^a	40/F/MBC	10 mg/kg/39 days	Primary reason of death: Respiratory distress and sepsis
168-0004/7311272 ^a	76/F/NSCLC	10 mg/kg/45 days	Acute respiratory failure, acute exacerbation COPD
208-0029/ 8041325	54/M/UC	10 mg/kg/19 days	Primary reason of death: Pneumonitis

COPD: chronic obstructive pulmonary disorder; GC: gastric cancer; MBC: metastatic breast cancer; NSCLC: non-small cell lung cancer, UC: urothelial cancer

^a The causality assessment reported is per the reporting investigator. The Sponsor evaluated 3 cases as not related at the time of reporting to health authorities (172-0004, 139-0004, and 168-0004).

Note: EMR 100070-001 is an ongoing trial. Safety data are not fully reconciled, therefore may be subject to change.

In Study 003, treatment emergent adverse events considered to be potential immune-related adverse events (irAEs) occurred in 13 patients (14.8%). In six patients (6.8%) the potential irAEs were assessed as related to avelumab and consisted of hypothyroidism in three patients (3.4%), hyperthyroidism in two patients (2.3%), and type 1 diabetes mellitus and pneumonitis in one patient (1.1%) each. All events were assessed as Grade 1 or Grade 2 in severity. Upon additional medical review, four other potential irAEs were identified as follows: Grade 3 increased transaminase (n=1); Grade 2 diarrhea (n=1); Grade 2 nephritis (n=1); and Grade 1 rash (n=1).

In Study 001, treatment emergent adverse events considered to be potential irAEs occurred in 149 patients (11.5%). In 99 patients (7.6%) the potential irAEs were assessed as related to avelumab (15 (1.2%) with Grade 3, five (0.4%) with Grade 4, and two (0.2%) with a fatal outcome). The two potential irAEs with a fatal outcome consisted of pneumonitis and radiation pneumonitis. Two additional patients with autoimmune hepatitis Grade 3 developed liver failure and died.

Proposed Confirmatory Trial: Study EMR 100070-006 (Study 006)

(b) (4)



Clinical Pharmacology

EMD Serono proposed to include the following clinical pharmacology data in the original BLA:

- Pharmacokinetic (PK) characteristics of avelumab after both single dose and multiple dose (Q2W) administration, including summary PK parameters and assessment of linearity and drug accumulation.

- Population PK analyses of three clinical trials to assess the influence of various intrinsic and extrinsic factors on the PK of avelumab. The intrinsic and extrinsic factors to be explored include age, ethnicity, gender, body size, race, tumor burden, tumor type, renal function, hepatic function, immunoglobulin, immunogenicity, and concomitant medications. In particular, the effect of body size on exposure will be investigated to understand the variability of PK across different body sizes within the context of exposure, efficacy/safety response in support of the dosing approach.
- Exposure-response for efficacy and safety analyses to support the dosing regimen.
- Incidence and duration of immunogenicity and assessment of its effect on PK, safety and efficacy.
- A summary of QTc results and an exposure-QTc analysis.
- An assessment of drug-drug interaction potential of avelumab as a victim using a population PK approach and analysis of the effect of avelumab on circulating cytokines in the clinical trials.
- Summary of PK and ADA results for Process A and Process B materials used in the three clinical trials.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

EMD Serono's position on Question #1 provided in Section 9.1 of briefing package.

1. **Does FDA agree the data from study EMR100070-003 (Part A) are sufficient to support the filing of a marketing application for the proposed indication under the accelerated approval provisions of 21 CFR 601 subpart E?**

FDA Response: Yes, the data from Study 003, Part A, which demonstrated an ORR of 32% (95% CI 22, 43) with 92% of the responses durable for more than 6 months in patients who have progressed on or following prior chemotherapy, are sufficient to support the filing of a licensing application submitted under the provisions of 21 CFR 601 subpart E.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

EMD Serono's position on Question #2 provided in Section 9.2 of briefing package.

2. **Per the study protocol, EMR 10007-003, the primary analysis was conducted 6 months after the accrual of the last subject (March 3, 2016); a further exploratory analysis will be conducted 12 months after the accrual of the last subject (September 3, 2016). The Sponsor is prepared to provide this exploratory analysis at the time of the submission of**

the 90-day safety update report provided the FDA agrees this submission will not extend the review clock. Does FDA agree with this proposal?

FDA Response: FDA does not object to conducting an exploratory analysis of the response data at the 12 month time point; however, EMD Serono should clarify the details of the exploratory analysis to be conducted and the purpose of such analysis.

EMD Serono's Response (Received via email on June 15, 2016): The 12 month exploratory analysis on the N=88 ITT population is being conducted to further characterize the durability of response. The planned analyses will include BOR, duration of response and response status at 12 months. Updated PFS and OS analyses are also planned.

Discussion During Meeting: FDA agreed that it would be acceptable to submit updated information on IRC-determined response duration concurrent with the 90 day safety update.

EMD Serono's position on Question #3 provided in Section 9.3 of briefing package.

3. Does FDA agree the proposed confirmatory trial design is sufficient to verify clinical benefit as required under 21 CFR 601 subpart E?

FDA Response:

(b) (4)

It is again noted that FDA expects that the confirmatory trial will be ongoing at the time the BLA is submitted.

EMD Serono's Response (Received via email on June 15, 2016): As communicated in the June 3, 2016 protocol amendment (reference IND 119,394 SN 0275), EMD Serono is committed to conducting a confirmatory study

(b) (4)

with the anticipation that EMR100700-003 will support the approval of a Biologic License Application (BLA) under 21 CFR Subpart E (accelerated approval) based on a surrogate endpoint. We have identified sites and are working expeditiously to open the trial.

EMD Serono's position on Question #4 provided in Section 9.4 of briefing package.

4. The analyses intended for the Integrated Summary of Safety (ISS) are specified in the statistical analysis plan (SAP):

a. Does FDA agree the proposed analyses in the ISS SAP are sufficient to support the BLA?

FDA Response: Yes, the analyses proposed for the ISS appear sufficient to support filing of the BLA. For Study 003, however, justify the proposed data cut-off as well as the exposure data intended for submission in the BLA. FDA expects that the data cut-off will be more current than that provided in the briefing document. Should any unexpected safety signals be identified during review of the BLA, additional analyses may be requested by FDA during review of the BLA. In addition, please clarify the data cut-off for Study 001.

EMD Serono's Response (Received via email on June 15, 2016): For study EMR100070-003 the data cut-off date (March 3, 2016) is approximately 6 months prior to the anticipated submission of the BLA submission date for both safety and efficacy. Exposure summaries per the proposed cut-off date for the BLA are provided in the following table (November 20, 2015 for EMR100070-001; March 3, 2016 for EMR100070-003).

Characteristic	Statistics	EMR100070-001 (N=1452) N (%)	EMR100070-003 (N=88) N (%)	Total (N=1540) N (%)
Number of subjects treated		1452	88	1540
Person-time exposure per 100 years		3.73	0.36	4.09
Number of subjects per treatment duration (%)	>3 Months	465 (32.0)	45 (51.1)	510 (33.1)
	>6 Months	170 (11.7)	34 (38.6)	204 (13.2)
	>12 Months	63 (4.3)	6 (6.8)	69 (4.5)
Treatment duration (weeks)	Median	11.9	17.0	11.9
	Q1; Q3	6.0; 18.0	7.4; 37.0	6.0; 18.0
	Min; Max	2.0; 107.9	2.0; 76.0	2.0; 107.9

We would like to clarify the data cut-off dates for studies to be included in the BLA, specifically:

Study	Clinical Database Cut-off	ARISg Data Cut-off (Additional CIOMS and Line Listings)
EMR100070-003	March 3, 2016 (both safety and efficacy)	April 30, 2016
EMR100070-001	November 20, 2015	April 30, 2016
EMR100070-002	November 20, 2015	April 30, 2016
Ongoing PH 3 Trials	NA	April 30, 2016

The November 20, 2015 data cut-off for study EMR100070-001 reflects the much larger database and the complexity of the global trial (over 200 sites and over 1400 patients), therefore, the time for validation of the data is extended.

Any significant late breaking safety information affecting the overall safety profile of avelumab received after the ARISg database cut-off date (April 30, 2016) through approval of the internal document in the company's electronic document management system will be evaluated and described in the Summary of Clinical Safety.

Discussion During Meeting: FDA agreed that the safety database cutoffs as displayed in the table above and in EMD Serono's response, including the data cutoff for SAEs of 4/30/2016, is acceptable. FDA requested, and EMD Serono agreed, that the BLA will contain additional analyses of safety in the subset of patients enrolled at least 3 months prior to the data cutoff dates above for key safety tabulations and analyses (all AEs, all Grade 3/ 4 AEs, all SAEs, and all AESIs).

b. Does FDA agree with the proposed analyses of adverse events of special interest (AESI) for the ISS?

FDA Response: Overall, selection of MedDRA terms for case review on irAEs appears generally adequate. However, FDA requests that EMD Serono include hypogonadism-related terms in immune-related endocrinopathy events. Also, EMD Serono should implement a vigorous review process for immune-related endocrinopathy events so as to distinguish secondary hypofunction of thyroid, adrenals and gonads due to hypopituitarism/hypophysitis from primary hypofunction of these glands.

In the original BLA submission as well as the safety update, provide patient narratives for all new irAEs, not only for serious or $\geq$ Grade 3 events. The narratives should capture why the adverse event was categorized as immune-related. Additionally, provide case report forms for all adverse events of special interest for studies EMR100070-001, EMR100070-002 and EMR100070-003.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono conducted a manual review of the clinical dataset that will serve to support the BLA; no AEs of hypogonadism were found using the following six terms: Hypogonadism, Hypogonadism female, Hypogonadism male, late onset hypogonadism syndrome, Primary hypogonadism and Secondary hypogonadism. EMD Serono will include these six terms prospectively in future immune-related safety sets. Additionally, EMD Serono will implement modifications to the endocrinopathy treatment algorithms to ensure the workup distinguishes primary endocrine dysfunction from secondary endocrine dysfunction.

We will provide patient narratives for all irAEs that meet the new structured case definition. The narratives will indicate the reason for suspicion of being immune-mediated.

Furthermore, we would like to clarify that for the BLA we plan to submit all deaths due to AEs regardless of attribution, however, for the safety update we intend to submit fully authored patient narratives for related TEAEs leading to death, IRRs (serious and/or $\geq$ grade 3), and immune-mediated events. Line listings will be provided for all TEAEs leading to death and all related SAEs will be provided (not narratives and not CIOMS).

Discussion During Meeting: FDA stated that EMD Serono's proposal was acceptable other than the proposal to provide only line listings for fatal TEAE and related SAEs in the 90-day update. FDA requested, and EMD agreed to provide, a narrative in the form of a CIOMS report for all treatment-related SAEs per investigator, in the 90-day safety update.

EMD Serono's position on Question #5 provided in Section 9.5 of briefing package.

5. With regard to the analyses for the safety update to be submitted 90 days after the BLA submission is complete:

a. Does FDA agree with the proposed integrated analyses cut-off date and content for the 90-day safety update report?

FDA Response: Overall, the June 9, 2016 data cut-off and content for the 90-day safety update appear acceptable assuming that the BLA submission is not delayed beyond September 2016. As noted in the response to Question 4b above, provide patient narratives for all new irAEs not only for serious or $\geq$ Grade 3 events in the safety update; in addition, updated narratives should be provided where new clinical information regarding the previously reported irAE is available. The narrative should capture why the adverse event was categorized as immune-related.

EMD Serono's Response (Received via email on June 15, 2016): We will provide patient narratives for all irAEs that meet the new structured case definition. The narratives will indicate the reason for suspicion of being immune-mediated. We will also update narratives when new clinical information is available.

Discussion During Meeting: FDA acknowledged EMD Serono's response.

b. Does the FDA agree with the proposal to use the most updated MedDRA version at the time of the 90 days cutoff for analyses?

FDA Response: No. FDA recommends that EMD Serono use the same MedDRA version for the safety update as the MedDRA version used in the datasets contained in the original BLA application.

EMD Serono's Response (Received via email on June 15, 2016): We acknowledge FDA's recommendation and we propose to revert to the former MedDRA version for the reporting of safety data from the clinical database for the safety update to be consistent with the BLA. We note that due to pharmacovigilance reporting requirements, the safety database will continue to use the updated MedDRA version for the safety update.

Discussion During Meeting: FDA acknowledged EMD Serono's original proposal in the briefing package, and stated that this will be acceptable. FDA and EMD Serono agreed that unless there are clinically important differences in safety profile between the two datasets, the updated safety database will be available for reference but not be included in product labeling to avoid reanalysis of all safety data.

EMD Serono's position on Question #6 provided in Section 9.6 of briefing package.

- 6. The Sponsor intends to include a subset of images of scans among patients with response in the CSR for descriptive purposes; however the Sponsor does not intend to submit all the images or photographs that were the basis of IRC review as part of the BLA. Does the Agency agree with EMD Serono's proposal not to submit radiographic images from the independent radiology review at the time of the BLA submission, but to have them available upon request during the BLA review process?**

FDA Response: Yes, FDA agrees with EMD Serono's proposal not to submit radiographic images for all patients, except upon request.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

EMD Serono's position on Question #7 provided in Section 9.7 of briefing package.

- 7. Prior to the interdisciplinary pre-BLA meeting EMD Serono requested three separate Type B meetings with individual disciplines at FDA (i.e., clinical pharmacology, CMC and nonclinical) to reach agreement regarding the content and format for each section of the proposed BLA.**
- a. Does FDA confirm the agreement reached regarding sufficiency of the proposed clinical pharmacology package, as outlined in the meeting minutes dated April 18, 2016 (reference ID 3918665)?**

FDA Response: Yes.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

- b. Does FDA confirm the agreement reached regarding sufficiency of the proposed CMC package, as outlined in the final meeting minutes from the upcoming April 26, 2016 Type B meeting?**

FDA Response: Yes.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

- c. **Does FDA confirm the agreement reached regarding sufficiency of the proposed nonclinical package in response to EMD Serono's request for written responses only?**

FDA Response: Yes.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

EMD Serono's position on Question #8 provided in Section 9.8 of briefing package.

8. EMD Serono is proposing to submit the BLA in three pieces, as follows:

- **Module 4 (Nonclinical Study Reports): July 6, 2016**
- **Module 3 (Quality), Module 2.3 (Quality Overall Summary): September 2, 2016**
- **Module 5 (Clinical), Module 2.2 (Introduction), Module 2.4 (Nonclinical Overview), Module 2.5 (Clinical Overview) and Module 2.7 (Clinical Summary) Module 2.6 (Nonclinical written and tabulated summaries): September 7, 2016**

Does FDA agree with the proposed rolling submission timeline?

FDA Response: FDA agrees to the proposed schedule for submission of components of the BLA, provided in the Briefing Package and as described below:

Rolling Submission	Module	Targeted Submission Date
Nonclinical	MODULE 4: Nonclinical Study Reports	July 6, 2016
CMC	MODULE 3: Quality	September 2, 2016
Clinical, Summaries & Administrative	MODULE 1 Administrative Information and Prescribing Information	September 7, 2016
	MODULE 2.1 CTD Table of Contents	
	MODULE 2.2 CTD Introduction	
	MODULE 2.3 Quality Overall Summary	
	MODULE 2.4 Nonclinical Overview	
	MODULE 2.5 Clinical Overview	
	MODULE 2.6 Nonclinical Written and Tabulated Summaries	
	MODULE 2.7 Clinical Summary	
	MODULE 5: Clinical Study Reports including Integrated Summary of Safety	

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Post-Meeting Follow-Up : We refer to your May 17, 2016, pre-BLA meeting briefing document containing a proposed schedule for submission of components of the BLA for avelumab. As communicated in our Meeting Preliminary Comments letter, dated June 15, 2016, we have reviewed your proposal and accept your request and plan for submitting portions of the proposed application. These meeting minutes serve to also grant a rolling review.

If the Breakthrough Therapy designation for avelumab for the treatment of patients with mMCC whose disease has progressed after at least one previous chemotherapy regimen is rescinded, submission of portions of the BLA will not be permitted under this program. However, if you still have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

For further information regarding Breakthrough Therapy designations, please refer to the FDA *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*¹.

EMD Serono's position on Question #9 provided in Section 9.9 of briefing package.

9. **For the electronic submission, EMD Serono is planning to provide the Study Data Standardization Plan in Module 1.12.14.2 of the eCTD to describe the trials and data standards used. The Study Data Standardization Plan will be based on the template provided by FDA. Does FDA agree Module 1.12.14.2 is the appropriate place to submit the Study Data Standardization Plan?**

FDA Response: Yes.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

EMD Serono's position on Question #10 provided in Section 9.10 of briefing package.

10. The Sponsor is proposing an application orientation meeting with FDA after the BLA submission to outline the major components of the BLA. Does the agency agree with this proposal? If so, when would the Agency propose this meeting to occur?

FDA Response: The application orientation meeting should occur after submission of the final module to the full BLA but before the filing date. Please discuss available dates for the meeting with the RPM for this application.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

EMD Serono's position on Question #11 provided in Section 9.11 of briefing package.

11. The Sponsor considers the overall content meets the criteria to support the BLA submission. Does FDA agree?

FDA Response: In general, the overall content as proposed appears to be acceptable to support filing of the BLA. The adequacy of the data to support approval will be evaluated during the BLA review.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

EMD Serono's position on Question #12 provided in Section 9.12 of briefing package.

12. Does FDA agree with EMD Serono's proposals, as outlined in this briefing document?

FDA Response: See FDA Response to Question 11.

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Clinical

- 13. Please confirm that verbatim terms will be included in all safety datasets, including datasets for older studies that are mapped to more current versions of MedDRA based on lower level term (LLT).**

EMD Serono's Response (Received via email on June 15, 2016): EMD Serono confirms that verbatim terms will be included in all safety datasets as recommended by FDA. No further discussion is required.

Discussion During Meeting: No discussion occurred.

DISCUSSION ON THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application
 - o Reference the discussion regarding agreement on the content of a complete application as captured in the meeting minutes issued on April 18, May 24, and June 8, 2016, and as discussed during the meeting held on June 16, 2016.
 - o EMD Serono stated that the application will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for REMS occurred. Based on the information provided in the pre-meeting package, the Office of New Drugs and the Office of Surveillance and Epidemiology agree that inclusion of Risk Mitigation and Evaluation Strategies (REMS) is not required in the initial BLA submission for the purposes of filing. FDA will make a final determination regarding the need for REMS during the review of the BLA.
- Late submissions

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide* (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

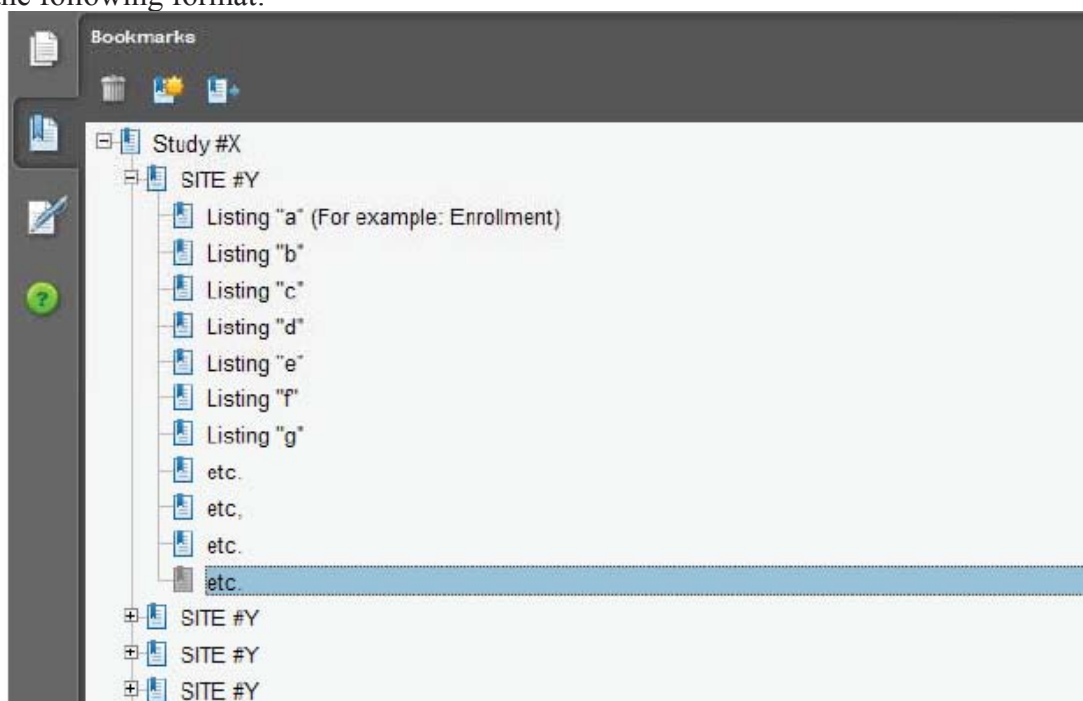
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item²	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

² Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

No attachments and handouts.

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

/s/

IDARA UDOH
07/06/2016



IND119394

**MEETING REQUEST-
WRITTEN RESPONSES**

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avelumab.

We also refer to your submission dated April 21, 2016, containing a Type B meeting request. The purpose of the requested meeting was to discuss the adequacy of the nonclinical package to support your proposed Biologic License Application (BLA) for avelumab for the proposed indication of the treatment of patients with metastatic Merkel cell carcinoma (mMCC) with disease progression after at least one previous chemotherapy regimen.

Further reference is made to our Meeting Granted letter dated May 5, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 2, 2016, background package.

APPEARS THIS WAY ON ORIGINAL

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Breakthrough Therapy-Other

Application Number: IND 119394
Product Name: Avelumab
Indication: Metastatic Merkel cell carcinoma (mMCC) with disease progression after at least one previous chemotherapy regimen
Sponsor/Applicant Name: EMD Serono, Inc.
Regulatory Pathway: §351 of the Public Health Service Act

MEETING PURPOSE

On April 21, 2016, EMD Serono, Inc. (“EMD Serono”) requested a Type B meeting, which included a briefing package, to discuss the adequacy of the nonclinical package to support a proposed Biologics License Application (BLA) for avelumab for the proposed indication of the treatment of patients with metastatic Merkel cell carcinoma with disease progression after at least one previous chemotherapy regimen.

EMD Serono plans to submit a BLA under the provisions of accelerated approval (21 CFR 601 Subpart E), which is supported by the results of a single trial, Study EMR100070-003, entitled “A Phase 2, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of MSB0010718C in Subjects with Merkel Cell Carcinoma (MCC),” seeking the proposed indication of the treatment of patients with metastatic Merkel cell carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen. EMD Serono is seeking clarity on the specific BLA components to gain early FDA feedback on pre-BLA activities, and plans to cover all aspects of the mMCC development program, including the nonclinical program.

EMD Serono requested FDA provide written responses in lieu of a face-to-face meeting, and FDA agreed that written responses would be the most appropriate means for responding to the meeting request. The Meeting Request Granted-Written Responses Only letter issued on May 5, 2016, and a revised briefing package was received containing missing data not included in the April 21, 2016, briefing package.

PROPOSED INDICATION

Avelumab is indicated for the treatment of patients with metastatic Merkel cell carcinoma (mMCC) with disease progression after at least one previous chemotherapy regimen.

BACKGROUND

Regulatory History

On January 14, 2014, a pre-IND meeting was held to discuss the proposed development program for avelumab for the treatment of patients with mMCC. At the time of the pre-IND meeting, EMD Serono had two, ongoing clinical trials assessing MSB0010718C in patients with solid tumors: Protocol EMR100070-001, being conducted under IND 115747, and a local Japanese trial, EMR100070-002. Protocol EMR100070-001 was a dose-finding and activity estimating trial; following determination of the recommended Phase 2 dose of 10 mg/kg every 2 weeks, the protocol proposed to enroll 150 patients each in the non-small cell lung cancer, gastric cancer and metastatic breast cancer cohorts and 20 patients each in the metastatic colorectal cancer, castrate resistant prostate cancer, advanced melanoma, and ovarian cancer cohorts. With regard to the proposed trial, (b) (4)



On March 4, 2014 a new IND was submitted, IND 119394, containing the clinical protocol for Study EMR 100070-003 (Study 003). The trial was designed as a single-arm, multi-center study of avelumab 10 mg/kg every 2 weeks to be conducted in 88 patients with mMCC who had received at least one line of previous chemotherapy. The primary endpoint of Study 003 was estimating of best overall response (BOR) as determined by RECIST v1.1.

On September 18, 2015, EMD Serono submitted a Breakthrough Therapy Designation (BTD) request for the treatment of patients with mMCC that have progressed after at least one previous chemotherapy regimen. Breakthrough Therapy Designation was granted on November 17, 2015.

On September 21, 2015, avelumab was granted orphan drug designation for the treatment of MCC.

On February 2, 2016, a Type B Breakthrough Therapy-Initial Comprehensive Multidisciplinary meeting was held to discuss plans to seek accelerated approval for avelumab for the treatment of patients with mMCC, to discuss plans to accelerate manufacturing development, and to reach agreement on the study design for the trial intended to verify clinical benefit. During this meeting, FDA recommended that EMD Serono schedule separate meetings with individual disciplines to discuss content and format issues for the proposed BLA prior to the interdisciplinary BLA meeting.

Clinical

EMD Serono is conducting Study 003 in patients with mMCC with disease progression following systemic chemotherapy. The primary endpoint for this study is confirmed objective response rate (ORR) according to RECIST 1.1., as determined by an independent review

committee (IRC). Response duration is the key secondary endpoint. EMD Serono intends to use the data from this study to support a BLA under the provisions of accelerated approval (21 CFR 601 subpart E).

EMD states that the safety of avelumab will be supported by the results of ongoing trials being conducted under other EMD Serono-sponsored INDs. As of November 5, 2015, 1300 patients with various cancers in the ongoing dose-finding with expansion study (Study EMR100070-001) received at least one infusion of avelumab at a dose of 10 mg/kg intravenously every two weeks. The median duration of exposure in the trial was 11.5 weeks (range 2 – 105 weeks).

Nonclinical

EMD Serono provided a list of studies to be included in the BLA. These studies included an assessment *vitro* and *in vivo* pharmacology, pharmacokinetics, cytokine release, tissue cross-reactivity, and phototoxicity. A GLP-compliant repeated-dose toxicity study was conducted in cynomolgus monkeys for 13 weeks with an 8-week recovery period. Genotoxicity and reproductive toxicity studies will not be conducted.

EMD SERONO'S QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the nonclinical package, as proposed, is sufficient to support the BLA filing?

FDA Response: The nonclinical package appears adequate to support the BLA filing; however, the acceptability of data from these studies will be determined during review of all data included in the original BLA. FDA reminds EMD Serono that while an embryofetal development study in non-human primates does not appear warranted, potential reproductive and development effects will need to be included in any marketing application. In addition, as discussed at the July 15, 2015 End-of-Phase 2 meeting, FDA recommends including any available data on the potential effects of avelumab on the immunologic recall or memory response.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of

your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

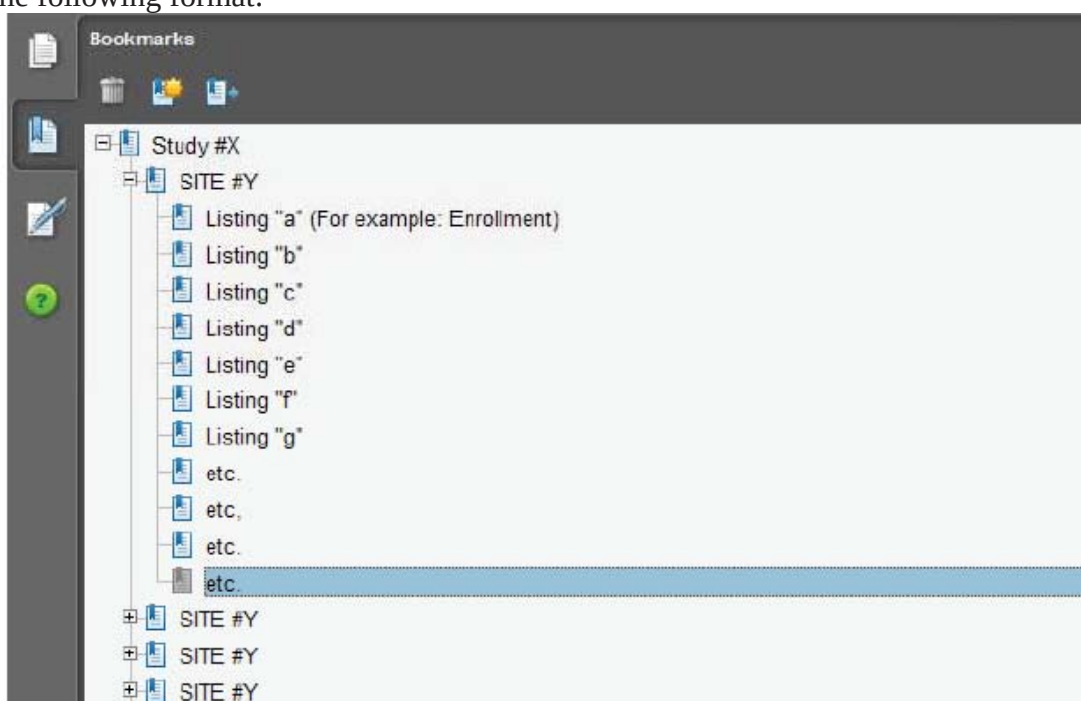
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

- b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing

Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

IDARA UDOH
06/08/2016



IND 119394

MEETING MINUTES

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

Dear Ms. Pappalardo,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avelumab.

We also refer to the meeting between representatives of your firm and the FDA on April 26, 2016. The purpose of the meeting was to discuss the content and format for the CMC sections of the proposed BLA (CTD Module 2.3 and Module 3).

A copy of the official minutes is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Joel Welch, Ph.D.
Team Leader
Division of Biotechnology Review and Research II
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: CMC Only

Meeting Date and Time: April 26, 2016 at 10 A.M.
Meeting Format Face to Face

Application Number: 119394
Product Name: avelumab
Sponsor/Applicant Name: EMD Serono, Inc.

Meeting Chair: Joel Welch
Meeting Recorders: Andrew Shiber

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Pharmaceutical Quality

Office of Biotechnology Products (OBP)/Division of Biotechnology Review and Research II

Joel Welch, Ph.D. Team Leader
Arulvathani Arudchandran, Ph.D. Product Quality

Office of Process and Facilities (OPF)/Division of Microbiology Assessment

Patricia Hughes, Ph.D. Acting Branch Chief
Bo Chi, Ph.D. Microbiologist

OPF/Division of Inspection Assessment

Steven Fong, Ph.D. Consumer Safety Officer

Office of New Drugs/Office of Hematology and Oncology Products

Idara Udoh Project Manager
Norma Griffin Team Leader

SPONSOR ATTENDEES

EMD Serono, Inc.

Herve Broly Vice President, Biotech Process Science
Isabelle Colmagne-Poulard, Ph.D. Head of Regulatory CMC
Ralf Gleixner, Ph.D., MBA Director, Regulatory CMC
Christian Hunzinger, Ph.D. Development Lead, CMC
Melanie Marmy Process Coordinator
Virginia Pappalardo Global Regulatory Lead
Achta Paraiso Le Bourhis, Pharm.D. Manager, Regulatory CMC
Mara Rossi Director, Protein Chemistry Department

Pfizer, Inc.

Marta Czupryn, Ph.D.

Chief Scientific Strategist

1. BACKGROUND

Name of drug: avelumab

Objectives: EMD Serono is looking for the Agency's feedback on the following:

- the approach for developing the avelumab control strategy;
- the implementation of FDA's recommendations received in the Type B CMC meeting held on December 19, 2014 (refer to FDA meeting minutes - reference ID 3709912 dated March 3, 2015) and the Type B meeting held on February 2, 2016 (refer to FDA meeting minutes - reference ID 3885457 dated February 10, 2016; and
- the overall content of the Quality modules of the Common Technical Document (Modules 2.3 and 3). 2.3 and 3).

2. DISCUSSION

Question 1:

Does FDA agree that the overall approach for developing the control strategy is adequate and allows sufficient control of the avelumab CQAs, in particular for the following attributes: Misincorporation (Asn to Ser Substitution; reference Section 9.1.1), Fc Effector Function (reference Section 9.1.2), Aggregates (reference Section 9.1.3), Fragments (reference Section 9.1.4) and Impurities Testing (reference Section 9.1.5).

9.1.1 Misincorporation (Asn to Ser Substitution)

Does FDA agree that the sponsor has gathered sufficient process understanding and has implemented an adequate process and materials control strategy for Asn to Ser substitution (b) (4)

No stability testing is being proposed as this attribute is not changing during product storage.

FDA Response to Question 1:

We cannot make a determination based on the data submitted. Preliminarily, we agree with your conclusion for the source of the misincorporation. However, review of the process validation data will be required to evaluate the adequacy of the control strategy. Additionally,

we request clarification on [REDACTED]

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback regarding misincorporation and confirms we will provide the process validation data (including process characterization data and process performance qualification data) in the BLA submission.

EMD Serono has confirm [REDACTED] t [REDACTED] of

(b) (4)

Meeting Discussion: The sponsor committed to include the comprehensive control strategy in the BLA submission. This will include [REDACTED]

(b) (4)

[REDACTED] The Agency agreed that if the data is sufficient then a final release test for Drug Substance would not be required.

Question 1.2:

Does FDA concur that the correlation between afucosylation and ADCC was sufficiently demonstrated by the Sponsor, and, therefore the inclusion of a direct ADCC testing control as an additional parameter for controlling the Fc effector function is no longer required? The sponsor proposes instead to include fucosylation testing within the avelumab Drug Substance release specifications. No stability testing is being proposed as this attribute does not change during product storage.

FDA Response to Question 1.2:

We agree that the data supports that afucosylation levels correlate with ADCC activity. Additionally, establishing a release test for glycosylation could be considered in lieu of ADCC activity on the release specification. Review of validation data for the glycan method will be required to make a final determination.

Sponsor Response:

EMD Serono acknowledges FDA's feedback. No further discussion is required.

NO MEETING DISCUSSION.

QUESTION 1.3:

Based on the data gathered by the Sponsor, does FDA concur that the aggregates could be removed from the Drug Substance specification and Drug Substance/ Drug Product stability testing? This parameter will be [REDACTED] in the Drug Product release specification.

(b) (4)

FDA Response to Question 1.3:

We cannot make a determination based on the data submitted. In principle, it may be possible to

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback regarding

(b) (4)

(b) (4) and will provide the requested justification in the BLA submission. No further discussion is required.

NO MEETING DISCUSSION.

QUESTION 1.4:

Based on the data gathered by the Sponsor, does FDA concur that the fragmentation monitoring could be removed from the avelumab Drug Substance specification? This parameter would be (b) (4) a release testing control for the avelumab Drug Product. It would be included in the Drug Substance and Drug Product stability testing.

FDA Response to Question 1.4:

We cannot make a determination based on the data submitted. As with the question in response

(b) (4)

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback regarding the fragment control strategy and will provide the requested justification in the BLA submission. EMD Serono would like to clarify that fragments will b

(b) (4)

a release testing control for the avelumab Drug Product. It will also be included in the Drug Substance and Drug Product stability testing.

Meeting Discussion:

The Agency agreed that the proposed considerations could be addressed in the BLA submission and support the sponsor's approach. The control strategy should integrate all of the elements such as: CQA and CPP's assessment as outlined above.

QUESTION 1.5:

Does FDA concur with the proposed

(b) (4)

FDA Response to Question 1.5:

Your proposal

(b) (4)

is considered appropriate. A final determination will be made at the time of BLA submission.

Sponsor Response:

EMD Serono acknowledges FDA's feedback. No further discussion is required.

NO MEETING DISCUSSION.

Additional FDA comment: The *(b) (4)* should be established as critical process parameters.

Sponsor Response:

EMD Serono acknowledges FDA's feedback

(b) (4)

Meeting Discussion: The Agency accepted the clarification from the sponsor.

QUESTION 2:

Does the FDA agree with the Sponsor's approach for bioburden and endotoxin testing?

(b) (4)

FDA Response to Question 2:

Based on the provided information, we have the following comments:

- *We recommend implementing in-process bioburden action limits for* (b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback and will implement the in-process bioburden action limits for (b) (4) ***No further discussion is required.***

NO MEETING DISCUSSION.

- (b) (4)
Provide the bioburden and endotoxin limits and the available storage verification data in Section 3.2.S.2.5 of the BLA.

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirm (b) (4) ***EMD Serono would like to clarify that this is considered a validation activity rather than routine testing. Does FDA agree?***

Meeting Discussion:

The Agency agrees that verification (b) (4) **is a validation activity rather than routine testing.**

- *The bioburden test volume should be 10 mL whenever feasible to improve the sensitivity of the bioburden test. The in-process bioburden limits and results should be expressed as CFU/volume tested.*

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirms the bioburden test volume will be harmonized to at least 10 mL and will express the results as CFU/volume tested. No further discussion is required.

NO MEETING DISCUSSION.

- *It is not clear if* (b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback

(b) (4)

o further discussion is required.

NO MEETING DISCUSSION.

- *We understand that*

(b) (4)

Please consider implementing this approach during the development of future manufacturing processes.

Sponsor Response:

EMD Serono acknowledges FDA's feedback and the approach will be considered for the development of future manufacturing processes. No further discussion is required.

NO MEETING DISCUSSION.

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirm

(b) (4)

oes FDA agree?

Meeting Discussion:

The Agency recommends to conduct a bioburden sampling as close as possible to the next step when feasible.

- *We recommend monitoring the bioburden and endotoxin of the*

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirm we will implement the monitoring of the bioburden and endotoxin

(b) (4)

No further discussion is required.

NO MEETING DISCUSSION.

- [REDACTED] (b) (4). *We recommend setting more meaningful alert limits based on bioburden trends from manufactured batches once sufficient data have been collected.*

Sponsor Response:

EMD Serono acknowledges FDA's feedback and will provide an update once sufficient data have been collected. We propose this update will be provided in the format of the Annual Report. Does FDA agree?

Meeting Discussion: The alert limits do not need to be provided in an Annual Report. They will be evaluated on inspections.

QUESTION 3:

Does the FDA agree with the Sponsor's strategy for validating [REDACTED] (b) (4)?

FDA Response to Question 3:

The drug product should be [REDACTED] (b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback and would like to further discuss the acceptability of our initial proposal [REDACTED] (b) (4)
EMD is requesting further discussion on this response.

Meeting Discussion:

The Agency agrees that the hold time is acceptable [REDACTED] (b) (4)

Post hold bioburden testing is not recommended.

Sponsor Response:

EMD Serono acknowledges FDA's feedback and wants to clarify [REDACTED] (b) (4)
Does FDA agree?

Meeting Discussion:

The Agency has accepted the clarification and the proposal is adequate.

QUESTION 4:

Does FDA agree that the activities performed by the Sponsor are sufficient to demonstrate that avelumab formulation does not interfere with endotoxin recoverability in the USP LAL test method over time?

FDA Response to Question 4:

The brief description of the endotoxin recovery study that was conducted appears to be adequate. The data will be evaluated during the BLA review process.

Sponsor Response:

EMD Serono acknowledges FDA's feedback. No further discussion is required.

NO MEETING DISCUSSION.

QUESTION 5:

Could the FDA PAI coincide with the Sponsor's 2016/2017 manufacturing campaign schedule?

FDA Response to Question 5:

The drug substance schedule for avelumab indicates that manufacturing will occur too late in the review cycle for a breakthrough submission. Please clarify the updated timing of the submission of the entire dossier. Typically, pre-license inspections for a breakthrough BLA are conducted in the second or third months of the BLA review cycle. Additionally, please identify the fill line used for drug product manufacturing.

Sponsor Response:

The BLA submission is planned for September 2016. Based on FDA's feedback where pre-license inspections for a breakthrough BLA are conducted in the second or third months of the review cycle, EMD Serono is investigating the possibility to reschedule the manufacturing campaign to November 2016. Does FDA agree with this proposal?

The fill line used for Drug Product manufacturing is (b) (4)

Meeting Discussion:

The Agency agrees with the proposal.

QUESTION 6:

Does FDA concur that the Sponsor's approach for manufacturing process validation is adequate to support the BLA submission?

FDA Response to Question 6:

Your proposed plan to demonstrate the manufacturing process validation seems appropriate. The final decision of the adequacy of the data will be a review issue.

Sponsor Response:

EMD Serono acknowledges FDA's feedback. No further discussion is required.

NO MEETING DISCUSSION.

QUESTION 7:

Does the FDA agree with the proposals made within the briefing document and with the overall content of the proposed CMC package?

FDA Response to Question 7:

Your proposed CTD format is acceptable. However, the adequacy of the information provided under each module in order to support your BLA is a review issue.

Sponsor Response:

EMD Serono acknowledges FDA's feedback. No further discussion is required.

NO MEETING DISCUSSION.

We have the following specific comments and recommendations with the proposed content:

- 1. With respect to the proposed shelf life, the proposed quantity of stability data is insufficient to support a 24-month shelf life for (b) (4) drug product. In order to support your proposed dating period you will need to provide a "simple stability update" during the course of the BLA review. A simple stability update is defined as: Stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission.*

Sponsor Response:

EMD Serono acknowledges FDA's feedback. The 24 month data will be available in November 2016 (two months after the BLA submission) and confirms a simple stability update will be provided during the course of the BLA review. Does FDA agree with this proposal?

Meeting Discussion:

The Agency agrees with the proposal.

- 1. The acceptance criteria and data for (b) (4) from microbiology perspective at scale should be provided in Section 3.2.S.2.5. See the second bullet point in FDA response to Question 2 above.*

Sponsor Response:

EMD Serono acknowledges FDA's feedback. Please refer to our response to Question 2 above.

NO MEETING DISCUSSION:

1. The [REDACTED] (b) (4)
[REDACTED] and the requalification program should be provided in
Section 3.2.P.3.5, not 3.2.A.1.

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirms the information will be included in section 3.2.P.3.5. No further discussion is required.

NO MEETING DISCUSSION.

2. In addition, please refer to the CMC Product Quality Microbiology comments below, which have been updated since the February 2016 meeting to assist product development:

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. An updated manufacturing schedule for the bulk drug substance and drug product fill finish sites should be included in Module 1 of the BLA.

Sponsor Response:

EMD Serono acknowledges FDA's feedback and will incorporate the requested information into module 1 of the BLA submission. No further discussion is required.

NO MEETING DISCUSSION.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

[REDACTED] (b) (4)

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's advice and confirms the product quality microbiology information will be provided in the BLA submission. No further discussion is required.

NO MEETING DISCUSSION.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the (b) (4) sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 "FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products".

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirms the requested information will be incorporated into the BLA submission. No further discussion is required.

NO MEETING DISCUSSION.

The following information related to (b) (4) should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirms the requested information will be incorporated into the BLA submission. No further discussion is required.

NO MEETING DISCUSSION.

Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

(b) (4)

Sponsor Response:

EMD Serono acknowledges FDA's feedback and confirms the requested information will be incorporated into the BLA submission. No further discussion is required.

NO MEETING DISCUSSION.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 these requirements. Please include a statement that confirms this finding, along with a

reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

ATTACHMENTS AND HANDOUTS

There were no handouts for the meeting.

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

/s/

JOEL T WELCH
05/24/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119394

MEETING MINUTES

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Senior Manager, Global Regulatory Affairs
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Pappalardo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avelumab (MSB0010718C).

We also refer to the teleconference between representatives of your firm and the FDA on April 15, 2016. The purpose of the meeting was to discuss the adequacy of the clinical pharmacology package to support a proposed Biologics License Application (BLA) for avelumab for the proposed indication of the treatment of patients with metastatic Merkel cell carcinoma with disease progression after at least one previous chemotherapy regimen and the acceptability of the proposed strategies for potential drug-drug interaction (DDI) and QTc risk assessment.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Breakthrough Therapy-Other

Meeting Date and Time: April 15, 2016; 11:30 AM – 12:00 PM
Meeting Location: Teleconference

Application Number: IND 119394
Product Name: Avelumab (MSB0010718C)
Indication: Metastatic Merkel cell carcinoma (mMCC) with disease progression after at least one previous chemotherapy regimen
Sponsor/Applicant Name: EMD Serono, Inc.

Meeting Chair: Hong Zhao, Ph. D.
Meeting Recorder: Idara Udoh, M.S.

FDA ATTENDEES

Center for Drug Evaluation and Research, Division of Oncology Products 2 (DOP 2)

Patricia Keegan, Director, Division of Oncology Products 2 (DOP 2)
Suzanne Demko, Clinical Team Leader, DOP 2
Idara Udoh, Senior Regulatory Health Project Manager, DOP 2
Anuja Patel, Senior Regulatory Health Project Manager, DOP 2

Center for Drug Evaluation and Research, Office of Clinical Pharmacology

Hong Zhao, Clinical Pharmacology Team Leader, DCPV
Sriram Subramaniam, Clinical Pharmacology Reviewer, DCPV

SPONSOR ATTENDEES

EMD Serono, Inc.

Jean-Marie Cuillerot, Global Head, Early Clinical Development Immuno-Oncology, EMD Serono, Inc.
Haiqing (Isaac) Dai, Director, Clinical Pharmacology, EMD Serono, Inc.
Lisa Mahnke, Medical Lead, EMD Serono, Inc.
Virginia Pappalardo, Global Regulatory Lead (MCC), EMD Serono, Inc.
Monika Rogozinska, Global Program Lead, EMD Serono, Inc.
Philippe Serrano, Head, Global Regulatory Affairs, EMD Serono, Inc.
Jennifer Stevens, Global Program Lead - Regulatory Affairs, EMD Serono, Inc.

Joleen White, Associate Director Quantitative Pharmacology & Drug Disposition, EMD Serono, Inc.

Pfizer

Carlo Bello, Senior Director Clinical Pharmacology, Pfizer, Inc.
Laurie Strawn, Global Regulatory Portfolio Lead, Pfizer

MEETING PURPOSE

On February 19, 2016, EMD Serono, Inc. (“EMD Serono”) requested a Type B meeting to discuss the adequacy of the clinical pharmacology package to support a proposed Biologics License Application (BLA) for avelumab for the proposed indication of the treatment of patients with metastatic Merkel cell carcinoma with disease progression after at least one previous chemotherapy regimen and the acceptability of the proposed strategies for potential drug-drug interaction (DDI) and QTc risk assessment.

EMD Serono plans to submit a BLA under the provisions of accelerated approval (21 CFR 601 Subpart E), which is supported by the results of a single trial, Study EMR100070-003, entitled “A Phase 2, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of MSB0010718C in Subjects with Merkel Cell Carcinoma (MCC),” seeking the proposed indication of the treatment of patients with metastatic Merkel cell carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen. EMD Serono is seeking clarity on the specific BLA components to gain early FDA feedback on pre-BLA activities, and plans to cover all aspects of the mMCC development program, including the clinical pharmacology program.

The teleconference was granted on March 1, 2016 and the meeting briefing package was received on March 17, 2016.

FDA sent Preliminary Comments to EMD Serono on April 12, 2016.

PROPOSED INDICATION

Avelumab is indicated for the treatment of patients with metastatic Merkel cell carcinoma (mMCC) with disease progression after at least one previous chemotherapy regimen.

BACKGROUND

Regulatory History

On January 14, 2014, a pre-IND meeting was held to discuss the proposed development program for avelumab for the treatment of patients with mMCC. At the time of the pre-IND meeting, EMD Serono had two, ongoing clinical trials assessing MSB0010718C in patients with solid tumors: Protocol EMR100070-001, being conducted under IND 115747, and a local Japanese trial, EMR100070-002. Protocol EMR100070-001 was a dose-finding and activity estimating trial; following determination of the recommended Phase 2 dose of 10 mg/kg every 2 weeks, the protocol proposed to enroll 150 patients each in the non-small cell lung cancer, gastric cancer and metastatic breast cancer cohorts and 20 patients each in the metastatic colorectal cancer, castrate resistant prostate cancer, advanced melanoma, and ovarian cancer cohorts. With regard to the proposed trial, (b) (4)

During the meeting, FDA also provided detailed advice regarding assessment of the pharmacology of avelumab.

On March 4, 2014 a new IND was submitted, IND 119394, containing the clinical protocol for Study EMR 100070-003 (Study 003). The trial was designed as a single-arm, multi-center study of avelumab 10 mg/kg every 2 weeks to be conducted in 88 patients with mMCC who had received at least one line of previous chemotherapy. The primary endpoint of Study 003 was estimating of best overall response (BOR) as determined by RECIST v1.1.

On August 25, 2015, EMD Serono submitted an initial draft protocol for Study EMR 100070-006 (Study 006), intended to provide confirmatory evidence of clinical benefit in patients with mMCC. (b) (4)

On September 18, 2015, EMD Serono submitted a Breakthrough Therapy Designation (BTD) request for the treatment of patients with mMCC that have progressed after at least one previous chemotherapy regimen. Breakthrough Therapy Designation was granted on November 17, 2015.

On September 21, 2015, avelumab was granted orphan drug designation for the treatment of MCC.

On December 18, 2015, EMD Serono submitted a revised protocol for Study 006 (b) (4)

(b) (4)

On February 2, 2016, a Type B Breakthrough Therapy-Initial Comprehensive Multidisciplinary meeting was held to discuss plans to seek accelerated approval for avelumab for the treatment of patients with mMCC, to discuss plans to accelerate manufacturing development, and to reach agreement on the study design for the trial intended to verify clinical benefit.

On March 23, 2016, EMD Serono submitted a new proposal containing revisions to Study 006.

(b) (4)

Clinical

EMD Serono is conducting Study 003 in patients with mMCC who have failed prior systemic chemotherapy. The primary endpoint for this study is confirmed objective response rate (ORR) according to RECIST 1.1., as determined by an independent review committee (IRC). Response duration is the key secondary endpoint. EMD Serono intends to use the data from this study to support a BLA under the provisions of accelerated approval (21 CFR 601 subpart E).

The safety of avelumab will be supported by the results of ongoing trials being conducted under other EMD Serono-sponsored INDs. As of November 5, 2015, 1300 patients with various cancers in the ongoing dose-finding with expansion study (Study EMR100070-001) received at least one infusion of avelumab at a dose of 10 mg/kg intravenously every two weeks. The median duration of exposure in the trial was 11.5 weeks (range 2 – 105 weeks).

Clinical Pharmacology

EMD Serono proposed to include the following clinical pharmacology data in the original BLA:

- Pharmacokinetic (PK) characteristics of avelumab after both single dose and multiple dose (Q2W) administration, including summary PK parameters and assessment of linearity and drug accumulation.
- Population PK analyses of three clinical trials to assess the influence of various intrinsic and extrinsic factors on the PK of avelumab. The intrinsic and extrinsic factors to be explored include age, ethnicity, gender, body size, race, tumor burden, tumor type, renal function, hepatic function, immunoglobulin, immunogenicity, and concomitant medications. In particular, the effect of body size on exposure will be investigated to understand the variability of PK across different body sizes within the context of exposure, efficacy/safety response in support of the dosing approach.

- Exposure-response for efficacy and safety analyses to support the dosing regimen.
- Incidence and duration of immunogenicity and assessment of its effect on PK, safety and efficacy.
- A summary of QTc results and an exposure-QTc analysis.
- An assessment of drug-drug interaction potential of avelumab as a victim using a population PK approach and analysis of the effect of avelumab on circulating cytokines in the clinical trials.
- Summary of PK and ADA results for Process A and Process B materials used in the three clinical trials.

EMD SERONO'S QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the clinical pharmacology package, as proposed to include the PK characteristics of avelumab, assessment of linearity and accumulation, PK summary between Process A and Process B, population PK, exposure-efficacy/safety analysis and assessment of immunogenicity, is sufficient to support the BLA submission?

FDA Response: Yes. The proposed clinical pharmacology package appears sufficient to support the BLA submission. The adequacy of the data will be evaluated at the time of the BLA review. FDA expects that all patients' samples that tested positive for binding anti-avelumab antibodies (ADAs) will also have been tested for neutralizing antibodies. Also, refer to Additional Comment 9.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's feedback on the overall sufficiency of the clinical pharmacology package to support the BLA submission with regard to the PK characteristics of avelumab, assessment of linearity and accumulation, PK summary between Process A and Process B, population PK and exposure-efficacy/safety analysis. EMD Serono would like to further discuss FDA's expectation that all subjects' samples that tested positive for ADAs will be tested for neutralizing antibodies.

Across clinical studies EMR100070-001, EMR100070-002, and EMR100070-003, the ADA response has been characterized for approximately 1500 patients. The overall ADA positivity rate is 4% based on interim data. The analysis of ADA impact on pharmacokinetics will be evaluated with pooled data across studies and the PopPK model.

Of the EMR100070-001 subjects who were treatment-emergent positive ADA or ever positive ADA, safety measures were evaluated relative to the rest of the subjects or never positive (Table 1). Within the restrictions of an unbalanced comparison, there was no clear difference. This analysis will be repeated for each of the above mentioned studies and the pooled integrated safety summary.

Table 1: Safety Subanalysis by Immunogenicity Status

Safety Measure	Treatment-emergent ADA vs. Rest ^a		Ever vs. Never Positive ADA ^a		All Patients (N=1398)
	Treatment-emergent (N=46)	Rest (N=1352)	Ever positive (N=53)	Never positive (N=1345)	
TEAE	46 (100%)	1270 (93.9%)	51 (96.2%)	1265 (94.1%)	1316 (94.1%)
Serious TEAE	25 (54.3%)	533 (39.4%)	28 (52.8%)	530 (39.4%)	558 (39.9%)
TE irAEs	7 (15.2%)	151 (11.2%)	8 (15.1%)	150 (11.2%)	158 (11.3%)
TE IRRs	13 (28.3%)	234 (17.3%)	14 (26.4%)	233 (17.3%)	247 (17.7%)

^aTreatment emergent ADA is all subjects without a positive baseline test and at least one positive post-treatment sample. Ever positive ADA is all subjects with at least one positive ADA, at either baseline or post-treatment.

Abbreviations: ADA anti-drug antibody, TEAE treatment emergent adverse events, TE irAE treatment emergent immune related adverse event, TE IRR treatment emergent infusion related reaction

No formal analysis of ADA impact on mMCC efficacy has been conducted to date. An informal evaluation was performed for the mMCC population in EMR100070-003 based on subject 206-0004, the only EMR100070-003 subject ever positive for immunogenicity at the November 2015 interim analysis. Subject 206-0004 had a partial response on day 44 and duration of response is ongoing (through day 295 as of interim analysis). If there are at least five ADA-positive subjects in EMR100070-003 at the time of the primary analysis, a formal analysis of the ADA impact on efficacy will be conducted.

At the time of the BLA submission, no neutralizing antibody (NAb) data will be available. An attempt to develop a cell-based assay did not result in a suitable assay for clinical analysis with sufficient sensitivity and drug tolerance. A new (b) (4) method is being developed with an anticipated validation completion in Q4 2016. We have completed initial proof of concept demonstrating that the polyclonal positive control antibody can interfere with the interaction between avelumab and PD-L1 target.

With a validation in Q4 2016, the NAb assay will be available in time to support the Phase 3 trials and the end of EMR100070-002. The protocols for EMR100070-001 and EMR100070-003 do not include NAb testing. For the orphan disease mMCC, EMD Serono proposes submitting NAb incidence and impact from EMR100070-006 in the post marketing setting. Does FDA agree with this proposal?

Discussion During Meeting: FDA agreed that because the product has Breakthrough Therapy Designation, the assessment for the incidence of neutralizing antibodies may be provided as a Post-Marketing Requirement (PMR). EMD should provide the proposed PMR, including all milestones, planned assessment of neutralizing antibodies in proposed studies, and justification for not testing retained samples from completed clinical trials.

2. Does the Agency agree with the proposed QTc analysis strategy and that a dedicated QTc study is not required for the BLA submission and for appropriate labeling of avelumab (pending review of the results)?

FDA Response: Yes. Also, refer to Additional Comments 6 and 18.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's feedback and no further discussion is required regarding the proposed QTc analysis strategy. EMD Serono is requesting further discussion regarding Comment 18 (please refer to the Company Response on page 6).

Discussion During Meeting: No discussion occurred.

3. Does the Agency agree that a dedicated DDI study is not required for the BLA submission and for appropriate labeling of avelumab (pending review of the results)?

FDA Response: Yes. Also, refer to Additional Comment 8.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Address the following clinical pharmacology related questions in the BLA submission:

4. What is the basis for selecting the avelumab dose and dosing regimen used in the registration trial?

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

5. What are the exposure-response relationships (dose-response, exposure-response) for efficacy and safety?

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

6. How was the QT prolongation potential of avelumab assessed? What are the conclusions and proposed labeling description?

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

7. What are the characteristics of distribution and elimination of avelumab?

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

8. What influence do the intrinsic factors (as listed below but not limited to) have on avelumab exposure, efficacy, safety and its pharmacodynamic response? What is their clinical impact? What influence do the extrinsic factors (e.g. concomitant medications, etc.) have on avelumab exposure and/or its pharmacodynamic response? What is their clinical impact?

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

9. What is the impact of immunogenicity (binding ADAs and neutralizing ADAs) on avelumab exposure and its efficacy and safety?

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request. Please refer to the company response provided to Question 1 above.

Discussion During Meeting: No discussion occurred.

In addition, please apply the following advice in preparing the clinical pharmacology sections of the BLA submission:

10. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies. Refer to the Guidance for Industry *Bioanalytical Method Validation* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

11. Submit the methods and validation reports for assays used for the detection of Binding and neutralizing anti-product antibodies. Refer to the Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf>.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

12. Provide complete datasets for clinical pharmacology and biopharmaceutics studies with the patients' ID numbers in the PK datasets consistent to those presented in the clinical datasets.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

13. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or patients that have been excluded from the analysis should be flagged and maintained in the datasets.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

14. Present the PK parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with range as appropriate in the study reports.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

15. Submit the following datasets to support the population PK analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation
 - A description of each data item provided in a Define.pdf file. Any concentrations and/or patients that have been excluded from the analysis should be flagged and maintained in the datasets
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
 - A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports, submit:

- The standard model diagnostic plots
- Individual plots for a representative number of patients. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1)
- A summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

16. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for the product in the targeted patient population and include the results of this exploratory analysis in the BLA submission. Refer to Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the exposure-response for PK versus best observed response and PK versus toxicity (AEs, irAEs, IRRs). EMD Serono will also provide PK versus target occupancy data, which we anticipate will be fully saturated throughout the dosing interval in the exposure range at the 10mg/kg dose.

Discussion During Meeting: No discussion occurred.

17. Submit the following items to support the exploratory exposure-response analysis for efficacy and safety
- Consider including the following when submitting the exposure-response analyses
 - Analyses may include but not limit to exploratory analysis such as Kaplan-Meier analyses stratified by subgroups of drug exposure, univariate and multivariate logistic and/or Cox regression analyses, whichever are deemed appropriate to support the dose selection or adjustment.
 - Drug exposure to be used in the analyses may include but not limit to trough concentration at steady state, maximum concentration at steady state, average concentration at steady state or trough concentration after first dose. A justification should be provided for the exposure metric that is used for the analysis.
 - Response should at least include primary and key secondary endpoints for efficacy, overall safety events, or adverse events of interest.
 - A model development flow chart, decision tree, or table that gives an overview of model development steps. Model codes and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model.
 - All datasets, NONMEM control streams, and scripts used for model development, validation, and simulation. Data files should be submitted as SAS transport files (e.g., Data1.xpt) and other files be submitted as ASCII text files (e.g., myfile_ctl.txt, myfile_out.txt)
 - Include the following in the exposure-response analysis reports
 - A summary of baseline characteristics including but not limit to demographics, disease features and lab measurements, for all patients used in the analysis and subgroups based on drug exposures
 - Distribution of drug exposure(s) for the full population used in analysis
 - A summary table of final model parameter with their corresponding units
 - Any plots deemed appropriate to support the clinical interpretation of modeling results
 - A summary describing the clinical application of modeling results.

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request and will provide the requested information in the BLA submission.

Discussion During Meeting: No discussion occurred.

18. Submit the following items for QTc study/assessment
- Copy of the clinical protocol
 - Copy of the Investigator's Brochure
 - Annotated CRF
 - A Define file which describes the contents of the electronic data sets
 - Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - A completed Highlights of Clinical Pharmacology Table

EMD Serono's Response (Received via email on April 14, 2016): EMD Serono acknowledges FDA's request to provide the abovementioned items for QTc assessment and will provide the requested information to support the BLA submission, however, EMD Serono would like to further discuss the request for ECG waveforms. Approximately 16,000 ECGs from 1,200 subjects were collected in Studies EMR100070-001, EMR100070-002 and EMR100070-003. A total of 228 trial sites were opened for enrollment and ECGs from enrolled patients were read and stored locally at the sites. A subset of ECGs with QTcF > 500 msec or change of baseline in QTcF >60 msec (about 147 on-treatment ECGs from 60 subjects, plus respective baseline ECGs) will be sent to a central laboratory for assessment. EMD Serono commits to providing this subset of ECG waveforms to the ECG warehouse, as requested. A portion of this subset will be scanned, as they are currently in paper format. Does FDA agree with the proposed subset of waveforms to be provided (QTcF > 500 msec or change of baseline in QTcF >60 msec)? Does FDA agree with submitting a proportion of waveforms as scanned paper?

Discussion During Meeting: FDA agreed that the proposal appears acceptable, but QT Interdisciplinary Review Team may have additional requests.

FDA recommends that EMD Serono provide detailed description of the process for assessment at local sites, auditing procedures to verify the accuracy of the data provided, and justification as to why these procedures ensure that an accurate assessment of incidence of increased QT has been obtained as soon as possible. If the QT assessment is deemed inadequate to fully assess risk, a PMR may be required.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies,

CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

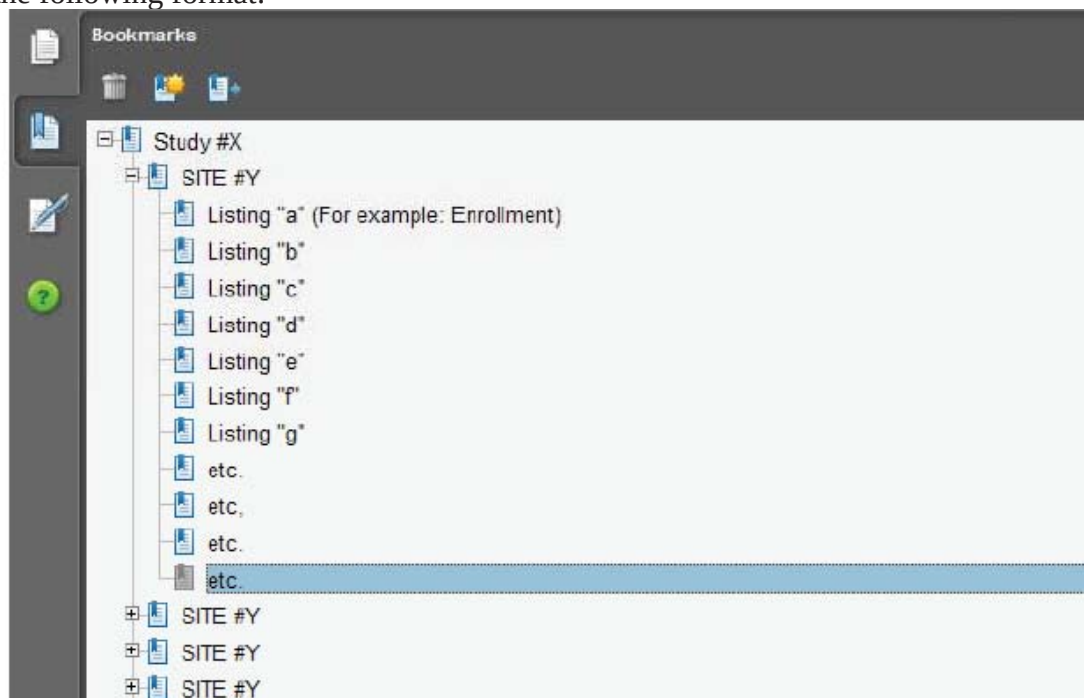
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number

- b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection

Planning” (available at the following link
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

No attachments or handouts.

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

/s/

IDARA UDOH
04/18/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119394

MEETING MINUTES

EMD Serono, Inc.
Attention: Virginia Pappalardo, RAC
Senior Manager, Global Regulatory Affairs
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Pappalardo:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avelumab (MSB0010718C).

FDA also refers to the meeting between representatives of your firm and the FDA on February 2, 2016. The purpose of the meeting was to discuss your plans to seek accelerated approval for avelumab for the treatment of patients with metastatic Merkel cell carcinoma (mMCC), to discuss your plans to accelerate manufacturing development, and to reach agreement on the study design for the trial intended to verify clinical benefit.

A copy of the official minutes of the February 2, 2016 meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Slides presented at the meeting by EMD Serono entitled, "IND 119394 Slides for FDA Presentation 020216 FINAL"



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Breakthrough Therapy-Initial Comprehensive Multidisciplinary
Meeting Date and Time: February 2, 2016; 2:00 PM – 3:30 PM, EST
Meeting Location: White Oak Building 22, Conference Room 1419
Application Number: IND 119394
Product Name: Avelumab (MSB0010718C)
Indication: Metastatic Merkel cell carcinoma (mMCC) with disease progression after at least one previous chemotherapy regimen
Sponsor/Applicant Name: EMD Serono, Inc.
Meeting Chair: Suzanne Demko
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Center for Drug Evaluation and Research, Division of Oncology Products 2 (DOP 2)

Patricia Keegan, Director
Suzanne Demko, Clinical Team Leader
Denise Casey, Clinical Reviewer
Idara Udoh, Senior Regulatory Health Project Manager
Karen Boyd, Acting Team Lead

Center for Drug Evaluation and Research, Division of Hematology Oncology and Toxicology (DHOT)

Whitney Helms, Nonclinical Team Leader

Center for Drug Evaluation and Research, Office of Clinical Pharmacology

Hong Zhao, Clinical Pharmacology Team Leader
Stacy Shord, Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biostatistics V (DBV)

Kun He, Statistical Team Leader
Pallavi Mishra-Kalyani, Statistical Reviewer

Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research II (DBRR-II)

Joel Welch, Product Quality Team Leader
Arulvathani Arudchandran, Product Quality Reviewer

Office of Pharmaceutical Quality, Division of Microbiology Assessment

Patricia Hughes, Branch Chief

SPONSOR ATTENDEES

EMD Serono, Inc.

Kevin Chin, Senior Medical Director, Immuno-Oncology, Global Research and Early Development
Jean-Marie Cuillerot, Global Head, Early Clinical Development Immuno-Oncology
Haiqing (Isaac) Dai, Director, Clinical Pharmacology
Lisa Mahnke, Medical Lead
Berend Neuteboom, Director, Global Early Development Lead
Virginia Pappalardo, Senior Manager, Regulatory Affairs, Immuno-Oncology
Monika Rogozinska, Senior Director, Global Program Lead
Shaliny Sarin, Manager, Regulatory Affairs, Immuno-Oncology
Jennifer Stevens, Regulatory Affairs, Immuno-Oncology

Ares Trading SA (An Affiliate of Merck Serono)

Isabelle Colmagne-Poulard, Head of Regulatory CMC
Ralf Gleixner, Regulatory CMC

Merck KGaA

Christian Hunzinger, CMC Development Lead
Armin Schueler, Head of Global Biostatistics, Oncology
Philippe Serrano, Head of Global Regulatory Affairs, Oncology
Isabell Speit, Medical Director, Global Drug Safety
Jacques Mascaro, PhD, Senior Vice President, Head of Global Regulatory Affairs and R&D Quality, Merck kGaA

Pfizer

Laurie Strawn, Global Regulatory Portfolio Lead

Additional Participant(s)

Paul Nghiem, Professor & Head, University of Washington Dermatology,

(b) (4)

MEETING PURPOSE

On December 4, 2015, EMD Serono, Inc. (“EMD Serono”) requested an Initial Comprehensive, Multidisciplinary Breakthrough Therapy Type B meeting to discuss the plans to seek accelerated approval for avelumab for the treatment of patients with mMCC, to discuss their plan to accelerate manufacturing development, and to reach agreement on the confirmatory study design intended to verify clinical benefit for the indication approved under accelerated approval.

EMD Serono is seeking clarity on the specific Biologic License Application (BLA) components to gain early FDA feedback on pre-BLA activities. EMD Serono plans to cover all aspects of the mMCC development program, including the nonclinical; chemistry, manufacturing, and controls (CMC); clinical; and clinical pharmacology programs.

EMD Serono proposes avelumab be indicated for the treatment of mMCC with disease progression after at least one previous chemotherapy regimen.

The meeting briefing package for this meeting was received on January 5, 2016.

FDA sent Preliminary Comments to EMD Serono on February 2, 2016.

BACKGROUND

Regulatory History

On November 13, 2013, IND 115747 was submitted to the Division of Oncology Products 2 for avelumab for the treatment of patients with various solid tumors. The IND was placed on partial hold on December 12, 2012 for insufficient information provided in the IND to assess whether the safety testing in the master cell bank (MCB) was sufficient to exclude contamination by (b) (4) [REDACTED] adventitious agent. The initial feasibility study was allowed to proceed; however, EMD Serono was required to provide data demonstrating that the MCB was free of adventitious agents (b) (4) [REDACTED]. This information was submitted on July 3, 2013, and the partial hold was removed on August 1, 2013.

On January 14, 2014, a pre-IND teleconference was held between FDA and EMD Serono to discuss the design of Study EMR 100070-003, entitled, “A Phase 2, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of MSB0010718C in Subjects with Merkel Cell Carcinoma (MCC).” This study is (b) (4) [REDACTED]

Based on this advice, EMD Serono proposed during the January 14, 2014, teleconference to conduct a study in a narrower patient population, i.e., patients who have progressed after they have received chemotherapy for the treatment of metastatic disease and patients with mMCC who are not suitable for treatment with chemotherapy because of underlying medical conditions. FDA provided the following feedback for this proposal:

- a) EMD would need to provide specific objective criteria for eligibility and justification based on available literature that this population has an unmet medical need, i.e. that objective responses could not be obtained with lower dose or alternative chemotherapy.
- b) The proposed approach may support full approval, accelerated approval, or no approval, and will depend on the results observed. EMD Serono would need to provide justification for the proposed effect size and duration of effect to be considered evidence of direct benefit or likely to predict clinical benefit based on a lower limit of the confidence interval observed around the response rate.
- c) Time-to-event endpoints will not be interpretable in a single arm trial. FDA requested that EMD Serono submit a proposal for a confirmatory study evaluating time-to-event endpoints for FDA review prior to initiating the study.

On March 4, 2014, the original IND 119394 was submitted including the clinical protocol for Study EMR 100070-003 (Study 003), a single-arm, multi-center study of avelumab in 88 patients with mMCC who have received at least one line of previous chemotherapy. The primary endpoint of Study 003 was estimating of BOR according to the RECIST 1.1 based on independent review of tumor assessments, with the aim of demonstrating that the estimated BOR was greater than 20% by the exact binomial test. A safe to proceed memo was issued on April 2, 2014.

A Type B meeting was held on December 14, 2014 to discuss the scale-up activities and comparability for Process B drug substance. Process B material is intended for phase 3 development and is the intended commercial drug substance manufacturing process. Data supporting the comparability was submitted to the IND on March 10, 2015 and deemed sufficient for introduction into clinical trials.

On June 12, 2015, a breakthrough therapy designation (BTD) preliminary advice form was submitted to FDA requesting a teleconference to discuss whether a request for BTD for mMCC was appropriate based on the data derived from the pre-specified futility analysis (n= 20 patients) that was performed during Study 003. A teleconference was held on July 1, 2015, and FDA recommended additional data on more patients with longer follow-up be included in the BTD request. FDA specifically recommended that the BTD request be submitted when EMD Serono had a minimum of three months, but preferably six months, of follow-up data on responders.

On August 25, 2015, EMD Serono submitted a draft protocol for Study EMR 100070-006 (Study 006), which is intended to provide confirmatory evidence of clinical benefit in patients with mMCC such that a potential indication for mMCC approved under accelerated approval could receive regular approval. (b) (4)



On September 18, 2015, EMD Serono submitted a BTD request for the treatment of patients with mMCC that have progressed after at least one previous chemotherapy regimen.

On September 21, 2015, avelumab was granted orphan drug designation for the treatment of MCC.

On October 1, 2015, Fast Track Designation was granted to EMD Serono for the investigation of avelumab for the treatment of patients with mMCC to demonstrate a clinically important and statistically robust improvement in PFS for patients treated with avelumab compared to available therapy.

On November 17, 2015 Breakthrough Therapy Designation (BTD) was granted to EMD Serono for the treatment of patients with mMCC who have progressed after at least one previous chemotherapy regimen.

Chemistry, Manufacturing, and Controls (CMC)

Avelumab drug product is a concentrated solution for intravenous use. The intended commercial presentation contains 20-mg/mL of avelumab in type 1 glass vials. The drug substance is (b) (4). The drug substance is manufactured in (b) (4) at Merck Serono in Vevey, Switzerland.

The initial clinical trial supply was supplied from drug substance manufacturing Process A, and was manufactured at (b) (4). The drug product was manufactured at Aubonne, Switzerland. The ongoing Study 003 utilizes drug substance with Process A material (b) (4). Process B material was introduced in Study EMR 100070-001 in April 2015 and was the material used in (b) (4).

Clinical

Disease Background

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other cutaneous malignancies by its expression of cytokeratin 20 (CK20). It is believed to arise from Merkel cells located in the basal layer of the epidermis though the cell of origin is still not definitive and the pathogenesis is not completely understood. MCC is a rare disease, but the annual incidence rate is increasing. Data from the Surveillance, Epidemiology and End Results (SEER) Program database estimated the annual incidence rate in 2006 as 0.6 per 100,000 persons. Factors associated with increased risk for developing MCC include ultraviolet (UV) radiation exposure, infection with the Merkel cell polyomavirus, and immunosuppression (e.g., organ transplant recipients, patients with HIV infection and B cell malignancies). The mean age at presentation is approximately 70 years of age.

Wide local surgical excision is the standard of care for localized MCC. Depending on the tumor location and the excision margins, adjuvant radiation may be administered following resection. For patients with disease present in local lymph nodes, the resection may include a wider dissection with lymphadenectomy, and adjuvant radiation is often administered. For patients with distant metastatic disease, chemotherapy regimens similar to those used for small cell lung cancer are used. The most common regimen is cisplatin or carboplatin in combination with etoposide; however, chemotherapy is generally tailored to the individual patient's age and baseline comorbidities. MCC tends to be a chemo-sensitive tumor; however, responses are not durable, and chemotherapy has not been shown to improve OS in patients with metastatic disease.

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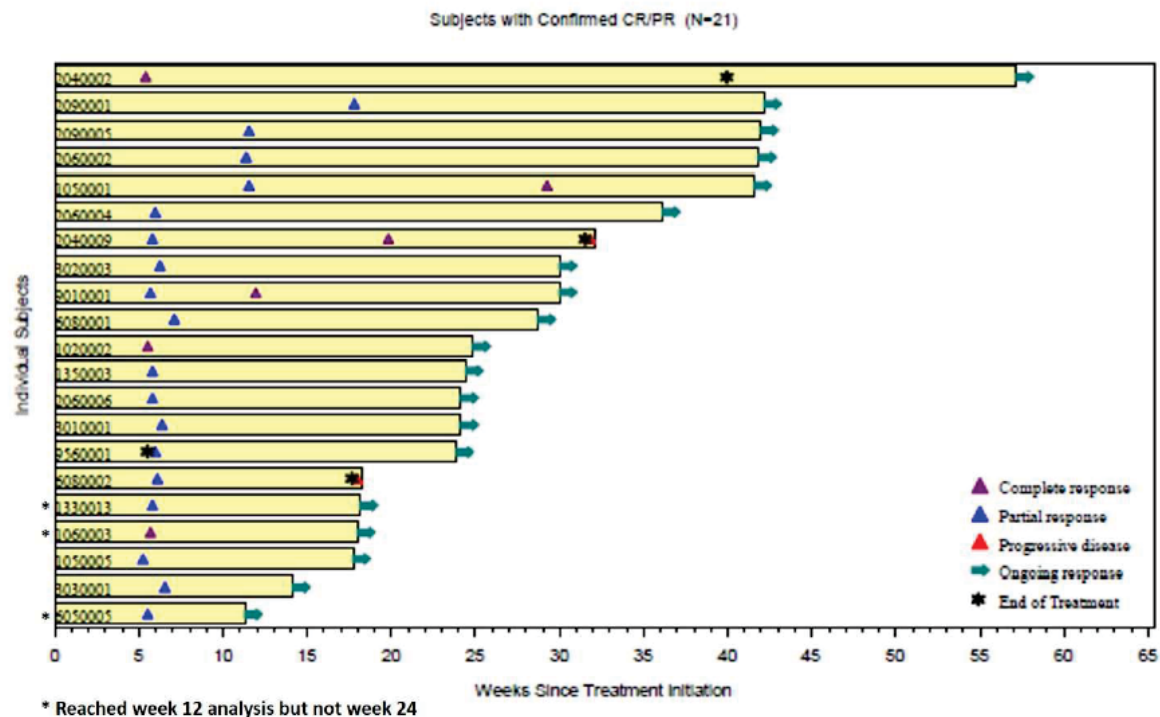
The 5-year survival rates for patients with MCC are 75%, 59%, and 25% for primary localized tumors, tumors with regional lymph node metastases (and/or local recurrences), and tumors with distant metastases, respectively. More than 30% of patients will develop distant metastatic disease. There are no large prospective studies reporting outcomes for patients with purely distant metastatic disease. A retrospective analysis of the treatment outcomes of 62 patients with MCC with distant metastases who were treated with frontline chemotherapy and the subgroup of 30 patients who received salvage chemotherapy at recurrence was recently published by Iyer et. al. The median OS for all patients was 9.5 months. Objective response rate with front-line chemotherapy was 54% (n=34). Among responders, the median duration of response (DOR) was 103 days (12-522 days). For the 30 patients who received salvage chemotherapy at recurrence, the ORR was 23% with a median DOR of 129 days (17-226).

Study EMR 100070-003(Study 003)

Study 003 is an ongoing, multicenter, open label, single arm study of avelumab in 88 patients with mMCC who have progressed following at least one previous course of chemotherapy. The primary endpoint for this study is confirmed ORR according to RECIST 1.1., as determined by an independent review committee (IRC). An interim efficacy analysis was completed in November 2015 when 56 patients had been treated for at least six months, and the final analysis is planned for March 2016, six months after the accrual of the last patient. EMD Serono intends to use the data from this study to support a marketing application for the proposed indication under the accelerated approval provisions of 21 CFR 601 subpart E. A summary of the available response rate and duration of response data in patients as of November 20, 2015 date was provided in Table 10 and Figure 8 copied below from the briefing document. Among the 18 patients (30%) with response in the 24 week analysis set, 16 are ongoing and 6 had duration at least 6 months.

Table 10: IRC Confirmed ORR by IRC by Duration of Follow-Up			
	Avelumab (n=88) ≥ 6 Weeks Follow-up	Avelumab (n=86) ≥ 12 Weeks Follow-up	Avelumab (n=61) ≥ 24 Weeks Follow-up
ORR (CR+PR), n(%); (95% CI)	21 (23.9); (15.4,34.1)	21 (24.4); (15.8, 34.9)	18 (29.5); (18.5, 42.6)
Complete Response	6 (6.8)	6 (7.0)	5 (8.2)
Partial Response	15 (17.0)	15 (17.4)	13 (21.3)
Stable Disease	9 (10.2)	9 (10.5)	7 (11.5)
Progressive Disease	28 (31.0)	28 (32.6)	23 (37.7)
Non CR/non PR	1 (1.1)	1 (1.2)	0
Not Evaluable	29 (33.0)	27 (31.4)	13 (21.3)

Figure 8: Time to and Duration of Response Determined by IRC Determination for Subjects with Confirmed Response with At Least 24 Weeks of Follow-up (N=18) with exception noted for three subjects meeting only 6 or 12 weeks of follow up (N=21)



EMD Serono is planning to amend Study 003 to incorporate a Part B cohort that would enroll an additional 50 patients with metastatic or distally recurrent MCC who are chemotherapy naïve. EMD Serono states that Part B will be open at sites mainly in the US (b) (4)

Avelumab Safety Profile

As of November 5, 2015, 1300 patients with various cancers in the ongoing dose-finding with expansion study (Study EMR100070-001) received at least one infusion of avelumab at the proposed dose of 10 mg/kg intravenous every two weeks. The median duration of exposure was 11.5 weeks (range 2-105 weeks). As of November 20, 2015, a total of 88 patients with mMCC were treated with at least one dose in Study 003. The median duration of exposure was 15 weeks (range 2- 60 weeks). Tables summarizing the treatment-related deaths and treatment emergent adverse events were provided in the briefing document and are copied here:

Table 14: Treatment-Related Deaths and the Events Leading to Deaths during Treatment Expansion in Trial EMR 100070-001

Subject ID/Mfr. Ctl No.	Age/Gender/Diagnosis	Avelumab Dose /Time on trial	Cause of Death
172-0004/7285199 ^a	71/F/NSCLC	10 mg/kg/ 10 days	Primary reason of death: Pneumonitis radiation induced and dyspnea (<i>downgraded to Grade 3 after data cut-off date</i>)
120-0014/7305891	51/F/MBC	10 mg/kg/ 46 days	Primary reason of death: Acute liver failure associated with autoimmune hepatitis (Grade 3) No biopsy/autopsy performed
102-0020/7265021	61/F/MBC	10 mg/kg/26 days	Fatal anoxic brain injury (not related) after cardiac arrest (related)
908-0003/7318782	50/F/GC	10 mg/kg/12 days	Primary reason of death: Autoimmune hepatitis (Grade 3) with hepatic failure and fatigue No biopsy/autopsy performed
139-0004/7319455 ^a	40/F/MBC	10 mg/kg/39 days	Primary reason of death: Respiratory distress and sepsis
168-0004/7311272 ^a	76/F/NSCLC	10 mg/kg/45 days	Acute respiratory failure, acute exacerbation COPD
208-0029/ 8041325	54/M/UC	10 mg/kg/19 days	Primary reason of death: Pneumonitis

COPD: chronic obstructive pulmonary disorder; GC: gastric cancer; MBC: metastatic breast cancer; NSCLC: non-small cell lung cancer, UC: urothelial cancer

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Table 11: EMR 100070-001 and -003: Most frequent TEAEs (all grades, in >10% of patients) and most frequent treatment related TEAEs, grade ≥3 – TEAEs sorted by descending order of frequency in EMR 100070-001 (TEAEs all grades)

	Avelumab 10 mg/kg every 2 weeks			
	Expansion Part Phase 1b (Various Solid Tumors) EMR100070-001 N=1300		Phase 2 Pivotal mMCC (EMR100070-003) N=88	
TEAEs (MedDRA Preferred Term (PT))	All Grades (n, %)	Treatment related Grade ≥3 (n, %)	All Grades (n, %)	Treatment related Grade ≥3 (n, %)
Subjects with at least one AE	1200 (92.3)	124 (9.5)	83 (94.3)	2 (2.3)
Fatigue	356 (27.4)	8 (0.6)	30 (34.1)	0
Nausea	276 (21.2)	1 (0.1)	17 (19.3)	0
Infusion related reaction	211 (16.2)	9 (0.7)	10 (11.4)	0
Diarrhoea	205 (15.8)	2 (0.2)	17 (19.3)	0
Constipation	204 (15.7)	2 (0.2)	14 (15.9)	0
Decreased appetite	194 (14.9)	3 (0.2)	16 (18.2)	0
Vomiting	188 (14.5)	3 (0.2)	10 (11.4)	0
Weight decreased	159 (12.2)	1 (0.1)	10 (11.4)	0
Abdominal pain	156 (12.0)	1 (0.1)	12 (13.6)	0
Anaemia	155 (11.9)	7 (0.5)	10 (11.4)	0
Cough	152 (11.7)	0	11 (12.5)	0
Dyspnoea	148 (11.4)	6 (0.5)	4 (4.5)	0
Pyrexia	148 (11.4)	0	6 (6.8)	0
Chills	137 (10.5)	1 (0.1)	9 (10.2)	0
Back pain	128 (9.8)	1 (0.1)	9 (10.2)	0
Arthralgia	122 (9.4)	2 (0.2)	13 (14.8)	0
Oedema peripheral	109 (8.4)	1 (0.1)	12 (13.6)	0
Asthenia	87 (6.7)	3 (0.2)	10 (11.4)	0
Hypertension	69 (5.3)	2 (0.2)	9 (10.2)	0
Pain in extremity	56 (4.3)	0	12 (13.6)	0
Transaminases increased	8 (0.6)	3 (0.2)	1 (1.1)	1 (1.1)
Blood creatine phosphokinase increased	14 (1.1)	3 (0.2)	2 (2.3)	1 (1.1)
Blood cholesterol increased	2 (0.2)	0	1 (1.1)	1 (1.1)

Note: EMR 100070-001 and -003 are ongoing trials. Safety data are not fully reconciled, therefore may be subject to change.

In Study 001, treatment emergent adverse events considered to be potential immune-related adverse events (irAEs) occurred in 149 patients (12%). Two potential irAEs with fatal outcomes consisting of pneumonitis and radiation pneumonitis in two separate patients occurred. Two patients with grade 3 autoimmune hepatitis thought to be drug-related developed liver failure and died.

Study EMR 100070-006 (Study 006)

Study 006 is the proposed confirmatory trial intended to verify clinical benefit of avelumab in patients with mMCC. (b) (4)



Clinical Pharmacology

EMD Serono proposed to include the following clinical pharmacology data in the original BLA:

- Pharmacokinetic (PK) characteristics of avelumab after both single dose and multiple dose (Q2W) administration, including summary PK parameters and assessment of linearity and drug accumulation.
- Population PK analyses of three clinical trials to assess the influence of various intrinsic and extrinsic factors on the PK of avelumab. The intrinsic and extrinsic factors to be explored include age, ethnicity, gender, body size, race, tumor burden, tumor type, renal function, hepatic function, immunoglobulin, immunogenicity, and concomitant medications. In particular, the effect of body size on exposure will be investigated to understand the variability of PK across different body sizes within the context of exposure, efficacy/safety response in support of the dosing approach.
- Exposure-response for efficacy and safety analyses to support the dosing regimen.
- Incidence and duration of immunogenicity and assessment of its effect on PK, safety and efficacy.
- A summary of QTc results and an exposure-QTc analysis.
- An assessment of drug-drug interaction potential of avelumab as a victim using a population PK approach and analysis of the effect of avelumab on circulating cytokines in the clinical trials.

EMD SERONO'S QUESTIONS AND FDA RESPONSES

Clinical

1. **Based on the recent FDA approval of Imlygic (talimogene laherparepvec), a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery, that was based on the primary endpoint of durable response rate (DRR), EMD Serono seeks FDA guidance on the utility of this endpoint in the MCC clinical development program, in particular when considering the clinical design of the ongoing Phase 2 Study (EMR100070-003) and the proposed confirmatory study (EMR100070-006).**

FDA Response: In general, a treatment effect demonstrating an objective response rate, as determined by an IRC, of sufficient magnitude and durability in the patient population of interest may be considered reasonably likely to predict clinical benefit. The patient population treated, the safety profile of the drug, and other therapies available to patients are also considered for regulatory decision making.

In order to file an application seeking accelerated approval for avelumab for the treatment of patients with recurrent mMCC who have progressed after at least one previous chemotherapy regimen based on the results of Study 003, the observed response rate and DOR should be of sufficient magnitude to conclude that avelumab is reasonably likely to provide clinical

benefit, and the results will be weighed against the safety risks observed. In order to verify clinical benefit as required under 21 CFR 601 Subpart E, a confirmatory trial demonstrating a treatment effect on OS or an improvement in PFS of a substantial and clinically meaningful magnitude would be acceptable.

An improvement in durable response rate, as defined in the briefing document, would be highly unlikely to provide direct evidence of clinical benefit. The durable response rate endpoint used to support the imlygic marketing application was considered in the context of the totality of clinical data demonstrating clinical benefit (response rate, cosmetic improvement of skin lesions and achieving surgical resectability) and the overall risk-benefit profile of the product. Imlygic is a localized treatment for cutaneous and subcutaneous melanoma lesions that is not intended to improve survival or have an effect on bone or visceral metastatic disease, and it poses relatively low risk for causing significant acute and long-term systemic toxicities as compared to the toxicity profile for a PD-1 inhibitor product. If EMD Serono plans to seek labeling claims based on durable response rate as defined above as a secondary endpoint in Study 006, a pre-planned statistical hierarchical testing strategy would be required for the analyses of the primary endpoint and selected key secondary endpoints.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback and agrees with the agency's position on durable response rate.

EMD Serono would like to discuss the latest available data (ORR, DOR) in the light of sustained durability and tolerability of avelumab in the 2L mMCC population. The durable responses demonstrate clinical benefit in this rare disease with an unmet medical need. EMD would like to further discuss the concept of prediction of clinical benefit versus demonstration of direct clinical benefit.

Discussion During Meeting: FDA stated that while demonstration of a durable objective response rate which was better than available therapy may support a request for accelerated approval, an application seeking regular approval will need to provide evidence of clinical benefit, i.e., to show improvement in survival or in how patients feel or function.

2. Does FDA agree that the proposed confirmatory study design, EMR100070-006, is adequate to confirm clinical benefit as required under 21 CFR 601 Subpart E?

FDA Response: FDA agrees that a well-designed, well conducted, internally consistent, randomized trial demonstrating a statistically robust and clinically meaningful improvement in PFS for patients with mMCC treated with avelumab as compared to standard chemotherapy would be adequate in design to verify clinical benefit as required under 21 CFR 601 Subpart E.

With regard to the proposed efficacy analyses for Study 006:

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Product Quality

3. **Does FDA agree with the stepwise approach for submitting the CMC information? Specifically does FDA agree with the proposal to submit Module 3 and Module 2.3 (Quality Overall Summary) based on Stage 1 validation data to initiate FDA rolling review of the CMC section?**

FDA Response: EMD Serono's proposal to submit stage 1 validation data to initiate rolling review of the submission may be sufficient. The Stage 2 validation data may be submitted to the FDA no later than 30 days after submission of the final major component of the BLA, as a late minor component; however this question should be revisited at time of the pre-BLA meeting.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: No discussion occurred.

4. **Recognizing additional data will become available during the BLA review cycle, does FDA agree with the rolling CMC submission strategy? Specifically, that the proposed CMC package to be submitted in Q2-2016 will constitute a reviewable unit and submission of additional CMC data during the review cycle (if required by FDA) will not constitute a major amendment that would extend the PDUFA clock?**

FDA Response: See FDA response to Question 3. If the proposed stage 2 validation data is submitted within 30 days of the final major component of the BLA, it would be considered a minor component that would not constitute a major amendment. The agreement to submit this minor component within 30 days of the submission of the final major component of the BLA should be discussed and agreement captured in the pre-BLA meeting minutes. Additional CMC data submitted after BLA submission is complete may not be reviewed.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback and willingness to accept the submission on the basis of Stage 1 data. Due to the need to revise timelines as a consequence of the answer to question 5, EMD Serono suggests submitting a complete CMC section which will now also comprise:

- 3.2.S.2.5 Stage 2 data for 3 Drug Substance PPQ batches
- 3.2.P.3.5 Stage 2 data for 3 Drug Product PPD batches
- A.2 Virus clearance (b) (4).

EMD Serono proposes having the remaining batches produced under the PPQ protocol (additional 3 DS and 2 DP batches) available during the pre-approval inspection. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Regulatory

5. **Does FDA agree with the rolling BLA proposal including timing for submission (nonclinical in Q1 2016, CMC in Q2 2016 and clinical in Q3 2016) and that the BLA submission would be considered complete in September 2016, thus starting the PDUFA review clock?**

FDA Response: FDA does not object to EMD Serono's plan for a rolling BLA submission; however, the proposed timeline is not acceptable. The first module should not be submitted until the results of Study 003 (i.e., final analyses of ORR, DOR and high level safety data for 88 patients who have been followed for at least six months) have been presented and discussed at the pre-BLA meeting at which FDA will reach agreement with EMD Serono on the content and format of a complete application to be filed under the PDUFA V program.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback and commits to reviewing the primary analysis results of the 003 study with the Agency prior to submitting the first module of the BLA. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Integrated Summary of Safety (ISS)

6. **Does the Agency agree that the study population for the Integrated Summary of Safety (ISS) will include all safety data from patients who were treated with 10mg/kg avelumab single agent in EMR100070-001 (Phase 1 dose escalation and dose expansion phase study in multiple solid tumor types) and in EMR100070-003 (Phase 2 study in mMCC) and the proposed data cutoff dates for these studies are acceptable to satisfy the requirement for submission of an ISS? Please note that the Japan Phase 1 Study (EMR100070-002) is not proposed to be part of the pooling patient population for the ISS.**

FDA Response: Pooling the safety data from patients treated in Study 003 with data from patients treated with 10mg/kg avelumab in Study 001 for analyses included in the ISS is acceptable. EMD Serono's plan to not include data from Study 002 in the pooled analyses for the ISS is acceptable provided that safety data summaries from Study 002 are provided in the clinical study report included in Module 5.

With regard to the proposed November 20, 2015 data cut-off date for Study 003, given that the median duration of exposure for the approximately 1300 patients treated with avelumab 10 mg/kg in Study 001 was 11.5 weeks (range 2-105 weeks) as of November 5, 2015, note that insufficient exposure data at the time of filing the BLA may warrant a post-marketing

requirement (PMR) under 505(o) to assess and provide an adequate description of long-term toxicity risks related to the use of avelumab.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: No discussion occurred.

7. **Given that the scope of the ISS pooled dataset can fit within the Summary of Clinical Safety (Module 2 Section 2.7.4), safety data for the pooled safety analyses will be summarized in Module 2 Section 2.7.4 and supportive tables, listings and figures for the ISS pooled analyses will be included in Module 5 Section 5.3.5.3. Does FDA agree with this approach?**

FDA Response: FDA agrees with EMD Serono's proposal to split the ISS such that the narrative discussions of the integrated analyses be included in Module 2.7.4 (Summary of Clinical Safety) and the integrated tables, listings and figures be included in Module 5 Section 5.3.5.3 (Reports of Analyses of Data from More than One Study). Include the datasets for the pooled population in Module 5.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: No discussion occurred.

APPEARS THIS WAY ON ORIGINAL

8. Does the Agency agree with the proposed pooling and analyses strategies that will be included in the ISS including the proposed analyses for the adverse events of special interest?

FDA Response: FDA agrees with the proposed pooling of patients in Studies 001 and 003 for the ISS and the key safety parameters described in sections 8.1.4.8 and 9.1.8 of the briefing package to be analyzed for the ISS. Additionally, provide an analysis of dose delays due to treatment emergent adverse events and subgroup analyses by tumor type, avelumab dose and the product used (i.e. drug substance manufacturing process A or B). Please flag datasets accordingly for tumor type, dose, and the drug substance manufacturing process.

In addition to the proposed analyses for immune-mediated adverse events (AEs) associated with avelumab described in sections 9.1.8 of the briefing package, the ISS should include case definitions for immune-mediated adverse reactions (e.g. enterocolitis, hepatitis, pneumonitis, dermatologic events) with specific criteria used to distinguish these events from non-immune adverse events with similar symptoms and/or laboratory abnormalities. Criteria should include the treatment administered (dose and duration of corticosteroid use, need for additional immunomodulatory agents), additional interventions (e.g., biopsies, procedures), onset and duration of the event, requirement for dose modification or discontinuation, and other concurrent endocrinologic findings. Also propose a preferred terms MedDRA query that will be used to capture events potentially related to immune-mediate reactions. Prior to performing these analyses, submit the proposed case definitions for FDA review and agreement.

In addition to the proposed analyses for infusion-related reactions described in sections 9.1.8 of the briefing package, the ISS should include

- A time-frame for identifying AEs thought to be related to infusion-related reactions (i.e., 24 hours following infusion)
- The preferred terms MedDRA query used to capture AEs commonly observed as infusion-reactions, including but not limited to fever, rigors, flushing, cutaneous reactions, hypotension, dyspnea, wheezing, back pain, and abdominal pain
- Analysis of the incidence of infusion reactions by treatment cycle
- Analysis of interventions for management of infusion reactions, including medications administered, alterations of infusion rate, etc.
- Analysis of the incidence of infusion reactions in patients with a previous infusion reaction (i.e., re-challenge)

APPEARS THIS WAY ON ORIGINAL

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: FDA requested that EMD Serono provide a case definition for capturing immune-mediated adverse events, as MedDRA terminology is not sufficient. EMD Serono agreed to provide a proposal.

Safety Update Report

9. Does the FDA agree with the Sponsor's intention to submit a safety update on the studies included in the Integrated Safety of Summary three months after the last component of the rolling BLA has been filed (i.e. 90 days safety update instead of 120 days)? The proposed data cut-off date for the updated analysis is at the time of the BLA submission i.e. 90 days prior to submission of the safety update report.

FDA Response: EMD Serono's proposal to submit a safety update on the studies included in the ISS 90 days after the last major component of the rolling BLA has been submitted is acceptable.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Risk Evaluation and Mitigation Strategy (REMS)

10. Does FDA agree that based on the available safety information from the ongoing Phase 1 Study (EMR100070-001) of more than 1500 patients treated with avelumab at the proposed dose/schedule of 10 mg/kg once every 2 weeks across different tumor types, and the emerging safety data from the ongoing Phase 2 MCC pivotal study (EMR100070-003) the submission of a Risk Evaluation and Mitigation Strategy (REMS) will not be required for the BLA submission considering that the Sponsor's proposed risk management strategy does include a Medication Guide as part of the US product labeling?

FDA Response: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a REMS will be necessary to ensure that the benefits of avelumab outweigh its risks, and if it is necessary, what the required elements will be. FDA will determine the need for a REMS during the review of the application.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Integrated Summary of Efficacy (ISE)

- 11. Given that accelerated approval will be sought off of a single Phase 2 open-label study (EMR100070-003), does the Agency agree that no separate Integrated Summary of Efficacy (ISE) is necessary in Module 5 and that the Summary of Clinical Efficacy (Module 2, Section 2.7.3) can satisfy the requirement for the ISE?**

FDA Response: FDA agrees that the text for the ISE may be cross-referenced from Module 5 to the information contained in the Summary of Clinical Efficacy (SCE; Module 2, Section 2.7.3). The SCE should not exceed 400 pages. The remainder of the information required in the ISE should be provided in Module 5.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Patient Narratives

- 12. EMD Serono proposes supplying patient narratives for all patients who died while on study, SAEs, AESI and discontinuations, as described in the Sponsor position below. For selected categories patient narratives will be submitted in the format of CIOMS I Forms. Does the Agency agree with the company's proposed strategy for narrative presentation of adverse events in the clinical study reports and the respective sections of the CTD?**

FDA Response: The proposed plan to submit narratives for all deaths, serious adverse events (SAEs), adverse events of special interest (AESI), and discontinuations in the respective CSRs for Studies 003, 002 and 001 is acceptable.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono would like to clarify with the Agency the proposed narrative submissions for adverse events, as outlined in the table found on page 83 of the briefing document, also below. EMD Serono is seeking clarification regarding death cases not reported as AEs. In particular, EMD Serono is seeking clarification regarding death cases regarding progressive disease.

Discussion During Meeting: FDA clarified that narratives should be submitted for all deaths within 30 days of the last dose of avelumab or discontinuation of avelumab for any reason other than disease progression, as well as for any death described as treatment-related.

Laboratory Values

13. EMD proposes to report laboratory data, including tables, listings and figures, in Système International (SI) units only, rather than in SI and U.S. conventional units. For a specific subset of parameters integrated ADaM datasets for the ISS will additionally contain transformed results in conventional units. Does FDA agree with this approach?

FDA Response: The proposed approach for reporting laboratory data in SI units is acceptable. The plan to present both SI and U.S conventional units in the integrated ADaM datasets for the parameters listed in Table 23 in the briefing document is also acceptable.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Module 5: Natural History/Observational Study Data

14. The observational study consists of retrospective data from chart reviews as well as from academic registry data. Depending on the data source and due to data privacy reasons, subject level data may be available to the Sponsor in a de-identified (anonymized) way or potentially even only in an aggregate form (summary statistics), i.e., not as subject level data. The CDISC SDTM and ADaM data models have been developed for clinical trial data on individual patient level but not specifically for aggregate data. Based on this, the Sponsor plans to (b) (4)

. Does FDA agree with this approach?

FDA Response: The proposal to (b) (4) is not acceptable as these data should be included in the text for the ISE in order to put the study results in context; please note that this data may not be used for comparative labeling claims.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: No discussion occurred.

Communication Plan

The Sponsor proposes the following communication plan to discuss the avelumab MCC BLA filing:

(b) (4)

Additionally, as necessary, the Sponsor proposes open communication with the respective FDA Project Managers to consult when questions arise outside of the proposed communication plan.

15. Does FDA agree with the proposed communication plan?

FDA Response: No, the proposed communication plan is not acceptable.

- a. There is no need for a specific meeting to discuss submission plans for the proprietary name request.
- b. The protocol-specified interim analysis results from the ongoing Study 003 can be presented and discussed at the pre-BLA meeting (i.e., meetings #3 and #4 can be combined into one meeting). Note that presentation of the final high-level efficacy and safety results from Study 003 is also expected for the pre-BLA meeting such that the proposed meeting timeline will need to be revised (See FDA response #5).
- c. Any remaining CMC issues can be addressed at a CMC-specific meeting which should be requested and held prior to the pre-BLA meeting.
- d. Include the clinical pharmacology topics in the pre-BLA meeting. See Additional Comment #18.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges FDA feedback and would like to further discuss the proposed timing for the pre-BLA meeting and the option to schedule the meeting prior to having the primary analysis data. EMD Serono would also like to discuss the option for submission of the meeting request and briefing document in an expedited manner to minimize delay (i.e. submitting the briefing document 2 weeks in advance of the meeting rather than the traditional 4 weeks).

Discussion During Meeting: EMD Serono stated that the planned analysis of the primary endpoint will be available at the beginning of May 2016. FDA recommended that EMD Serono schedule separate meetings with individual disciplines (e.g. CMC, nonclinical) to discuss content and format issues for the proposed BLA prior to the interdisciplinary pre-BLA meeting.

ADDITIONAL FDA COMMENTS

Chemistry, Manufacturing, and Controls (CMC)

16. Please provide a detailed drug substance (DS) manufacturing schedule in your initial CMC module submission.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges the FDA feedback, and plans to incorporate the recommendation into its program development.

Discussion During Meeting: No discussion occurred.

Product Quality Microbiology

17. All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA to facilitate the planning of the pre-license inspections during the review cycle. Please include in the BLA a complete list of the manufacturing and testing sites with their corresponding FEI numbers.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:



(b) (4)



The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) sterility assurance. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products” at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>

The following information related to (b) (4) should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate:

(b) (4)



The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

(b) (4)



(b) (4)

The following method validation information should be provided:

(b) (4)

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges FDA feedback and will follow-up on any CMC questions at a CMC-specific meeting which will be requested prior to the pre-BLA meeting.

Discussion During Meeting: No discussion occurred.

Clinical Pharmacology

18. Provide a summary of the clinical pharmacology data to be included in the complete BLA including study reports and datasets in the multidisciplinary pre-BLA meeting package to reach agreement under the provision of the PDUFA V program.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: No discussion occurred.

19. Provide a tabular summary of the pharmacokinetics and safety data following administration of drug product manufactured using Process A material compared to that of drug product manufactured using Process B material at the proposed clinical dose of 10 mg/kg every two weeks in the pre-BLA meeting package.

EMD Serono's Response (Received via email on February 2, 2016): EMD Serono acknowledges FDA feedback, and plans to incorporate the recommendation into its program development. No further discussion is required.

Discussion During Meeting: No discussion occurred.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing

application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

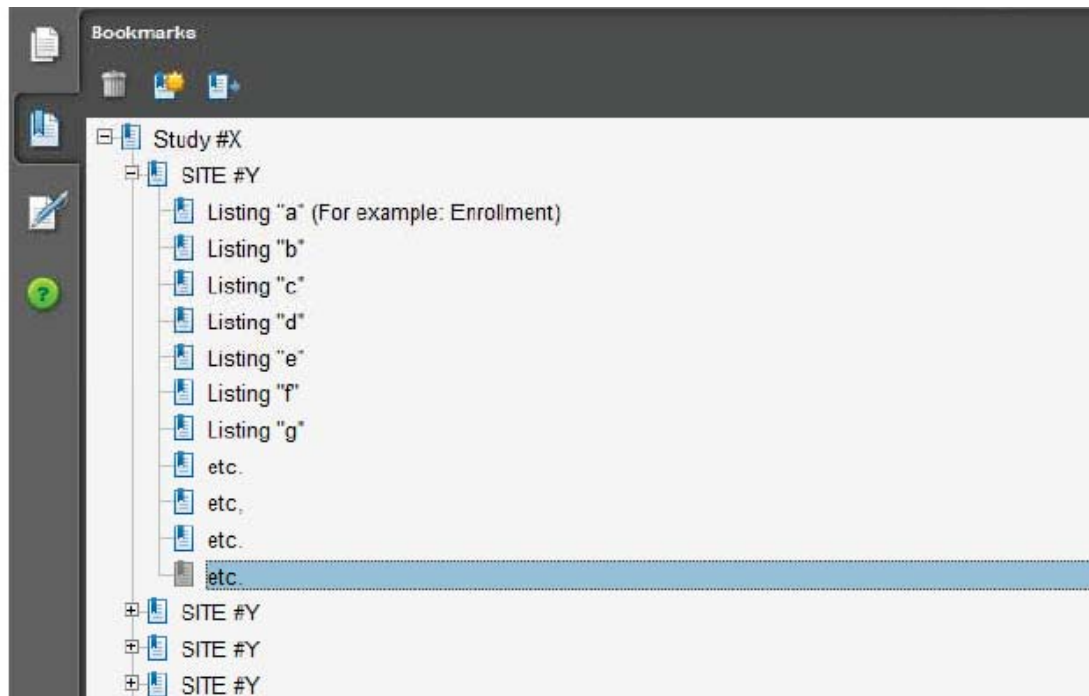
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

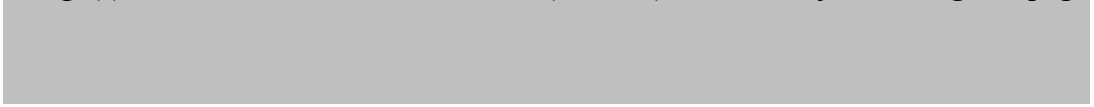
ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

“IND 119394 Slides for FDA Presentation 020216 FINAL” PowerPoint Slides

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



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

/s/

IDARA UDOH
02/10/2016

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 119394
Request Receipt Date	September 18, 2015
Product	Avelumab (MSB0010718C)
Indication	Metastatic Merkel cell carcinoma (mMCC) which has progressed after at least one previous chemotherapy regimen
Drug Class/Mechanism of Action	IGg antibody against programmed death ligand 1(PD-L1)
Sponsor	EMD Serono, R&D Institute, Inc.
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	November 17, 2015

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

The proposed indication for avelumab is for the treatment of patients with metastatic Merkel cell carcinoma (mMCC) which has progressed after at least one previous chemotherapy regimen.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold? ☐ YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹? ☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
 - ☐ Undetermined
 - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

N/A

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

² For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- **Information regarding the disease and intended population for the proposed indication.**
- **Disease mechanism (if known) and natural history (if the disease is uncommon).**

Disease Background

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine carcinoma of the skin, which can be distinguished from other cutaneous malignancies by its expression of cytokeratin 20 (CK20). It is believed to arise from Merkel cells located in the basal layer of the epidermis though the cell of origin is still not definitive and the pathogenesis is not completely understood.¹ MCC is a rare disease, but the annual incidence rate is increasing. Data from the Surveillance, Epidemiology and End Results (SEER) Program database estimated the annual incidence rate in 2006 as 0.6 per 100,000 persons. Factors associated with increased risk for developing MCC include ultraviolet (UV) radiation exposure, infection with the Merkel cell polyomavirus, and immunosuppression (e.g., organ transplant recipients, patients with HIV infection and B cell malignancies). The mean age at presentation is approximately 70 years of age.¹

Wide local excision with at least a 2-3cm minimum margin is the standard of care for localized MCC. Depending on the tumor location and the excision margins, adjuvant radiation may be administered following resection. For patients with disease present in local lymph nodes, the resection may include a wider dissection with lymphadenectomy, and adjuvant radiation is often administered.^{1,2} For patients with distant metastatic disease, chemotherapy regimens similar to those used for small cell lung cancer are used. The most common regimen is cisplatin or carboplatin in combination with etoposide, however, chemotherapy is generally tailored to the individual patient's age and baseline comorbidities.⁴ MCC tends to be a chemosensitive tumor; however, responses are not durable, and chemotherapy has not been shown to improve overall survival in patients with metastatic disease.

The 5-year survival rates for patients with MCC are 75%, 59%, and 25% for primary localized tumors, tumors with regional lymph node metastases (and/or local recurrences), and tumors with distant metastases, respectively.¹ More than 30% of patients will develop distant metastatic disease.⁵ There are no large prospective studies reporting outcomes for patients with purely distant metastatic disease, and many studies pool patients with locoregional with those having distant metastatic disease. A retrospective analysis of the treatment outcomes of 62 patients with MCC with distant metastases who were treated with frontline chemotherapy and the subgroup of 30 patients who received salvage chemotherapy at recurrence was recently published. The median overall survival (OS) for all patients was 9.5 months. Objective response rate (ORR) with front-line chemotherapy was 54% (n=34). Among responders, the median duration of response (DOR) was 103 days (12-522 days). For the 30 patients who received salvage chemotherapy at recurrence, the ORR was 23% with a median DOR of 129 days (17-226).³

Relevant Regulatory History

On January 14, 2014, a preIND teleconference was held between FDA and EMD Serono to discuss the design of Study EMR 100070-003, entitled, "A Phase 2, Open-label, Multi-center Trial to Investigate the Clinical Activity and Safety of MSB0010718C in Subjects with Merkel Cell Carcinoma." The initially proposed study was (b) (4)

[REDACTED]

(b) (4)

- o Based on this advice, during the teleconference EMD Serono proposed to alternatively conduct a study in a narrower population: patients who have progressed after they have received chemotherapy for the treatment of metastatic disease and patients with metastatic MCC who are not suitable for treatment with chemotherapy because of underlying medical conditions. FDA provided the following feedback to this proposal:
 - a) EMD would need to provide specific objective criteria for eligibility and justification based on available literature that this population has an unmet medical need, i.e. that objective responses could not be obtained with lower dose or alternative chemotherapy.
 - b) The proposed approach may support full approval, accelerated approval, or no approval, and will depend on the results observed. EMD Serono would need to provide justification for the proposed effect size and duration of effect to be considered evidence of direct benefit or likely to predict clinical benefit based on a lower limit of the confidence interval observed around the response rate.
 - c) Time-to-event endpoints will not be interpretable in a single arm trial. FDA requested that EMD Serono submit a proposal for a confirmatory study evaluating time-to-event endpoints for FDA review prior to initiating the study.

On March 4, 2014, the original IND was submitted including the clinical protocol for Study EMR 100070-003, a single-arm, multicenter study of avelumab in 84 patients with metastatic MCC who have received at least one line of previous chemotherapy. The primary endpoint is best overall response (BOR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 based on independent review of tumor assessments. The trial aims to demonstrate an ORR greater than 20% by the exact binomial test. A safe to proceed memo was issued on April 2, 2014.

On June 12, 2015, a breakthrough therapy designation (BTD) preliminary advice form was submitted to FDA requesting a teleconference to discuss whether a request for BTD for metastatic MCC was appropriate based on the data derived from the prespecified futility analysis (n= 20 patients) that was performed during Study EMR 100070-003. A teleconference was held on July 1, 2015, and FDA recommended additional data on more patients with longer follow-up be included in the BTD request. FDA specifically recommended that the BTDR be submitted when EMD Serono had a minimum of 3 months, but preferably 6 months, of follow-up data on responders.

On August 14, 2015, EMD Serono submitted a Fast Track Designation request (FTDR) for the treatment of patients with metastatic MCC who have progressed after at least one prior chemotherapy regimen.

On August 25, 2015, EMD Serono submitted a draft protocol for Study EMR100070-006 (Study 006), (b) (4)

Study 006 is intended to provide confirmatory evidence of clinical benefit in patients with metastatic MCC such that a potential indication for metastatic MCC approved under accelerated approval could receive regular approval.

On September 18, 2015, EMD Serono submitted a BTDR for the treatment of patients with mMCC which has progressed after at least one previous chemotherapy regimen.

On September 23, 2015, DOP2 had a teleconference with EMD Serono to discuss the proposed indication in the FTDR. FDA reminded EMD Serono that a Fast Track Designation encompasses the entire development program for a product. Given the August 25, 2015 submission including a draft protocol for a proposed confirmatory trial

(b) (4) DOP2 advised that EMD Serono request a broader indication for Fast Track Designation for avelumab without specifically addressing the line of therapy. This would allow flexibility to use the results from the ongoing study in chemotherapy-refractory patients to design the most appropriate subsequent studies. EMD Serono agreed.

On October 1, 2015, Fast Track Designation was granted to EMD Serono for the investigation of avelumab for the treatment of patients with metastatic MCC to demonstrate a clinically important and statistically robust improvement in progression free survival (PFS) for patients treated with avelumab compared to available therapy.

Avelumab: Mechanism of Action and Clinical Development in MCC

Avelumab is a fully human IgG1 antibody directed against PD-L1. Blockade of PD-L1 results in activation of CD8+ cytotoxic T cells. Avelumab also has effector functions and is capable of antibody-dependent cellular cytotoxicity (ADCC) against cells expressing PD-L1. The contribution of ADCC to clinical efficacy with avelumab and other immune therapies is not clear.

Avelumab is currently being investigated in four clinical trials, and over 1300 patients with various cancers have received avelumab. The recommended phase 2 dose (RP2D) established in the dose-finding Study EMR100070 for patients with refractory solid tumors was 10 mg/kg intravenously (IV) every two weeks.

There is one ongoing study in patients with metastatic MCC (EMR100070-003) entitled: "A Phase II, open-label, multicenter trial to investigate the clinical activity and safety of MSB0010718C in subjects with Merkel cell carcinoma." It is an open-label, single arm trial to evaluate the safety and efficacy of avelumab in 88 patients with metastatic MCC who have received at least one line of prior chemotherapy. Patients are receiving avelumab 10 mg/kg IV every two weeks. The primary endpoint is centrally reviewed best overall response (BOR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Duration of response will be evaluated as a secondary endpoint. The sample size of the trial is based on the assumption of a 35% objective response rate, and the trial aims to demonstrate an ORR greater than 20% using the exact binomial test. The primary analysis will be performed 6 months after the accrual of the last patient. An interim analysis for futility was completed in April 2015 after 20 patients were enrolled and observed for at least 3 months, and the futility criteria were not met. An interim analysis for efficacy is planned after 56 patients have been enrolled and observed for 6 months. According to the sponsor, the null hypothesis can be rejected if 20 patients in the interim analysis or 25 patients in the primary analysis experience a confirmed objective response according to RECIST 1.1.

EMD Serono recently submitted a draft protocol for FDA review for the planned Study EMR100070-006 (b) (4)

[REDACTED]

7. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

EMD Serono considers durable objective response rate to be a clinically meaningful endpoint supporting the BTDR. Overall response rate according to RECIST is the primary endpoint for Study EMR100070-003. Duration of response is a secondary endpoint. In the planned confirmatory trial, Study EMR100070-006, (b) (4)

[REDACTED]

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 agrees that demonstration of a meaningful effect size on durable objective response rate according to RECIST would be clinically meaningful and reasonably likely to predict clinical benefit of a drug in patients with metastatic MCC and could support an application for accelerated approval. (b) (4)

[REDACTED]

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s)

used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no FDA-approved therapies and no known curative treatments for patients with metastatic MCC. There is evidence in the literature that metastatic MCC is responsive to cytotoxic chemotherapy regimens similar to those used for small cell lung cancer; however, these responses have not been shown to be durable. The literature reports response rates to first-line chemotherapy as 50-60% with reduced response rates and durability in the second and third line setting. The median DOR observed in patients treated with first line chemotherapy is 3-9 months.^{3,6} Regimens used for patients with newly diagnosed metastatic MCC are carboplatin plus etoposide, cisplatin plus etoposide, single agent topotecan and less commonly, cyclophosphamide plus doxorubicin plus vincristine (CAV).⁴ Physicians generally choose a regimen based on the patient's age at presentation and baseline comorbidities. No regimen has been shown to be superior.⁴

The following table summarizes targeted agents that are currently being evaluated in clinical studies in patients with MCC with distant metastatic disease. Cytotoxic chemotherapeutics or drugs being evaluated in refractory all-comer cancer populations are not included.

(b) (4)

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

No other drugs have received breakthrough therapy designation for this indication.

10. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The data supporting the BTDR for avelumab comes from Study EMR 100070-003. This is an ongoing multicenter, single arm, study of avelumab 10 mg/kg IV every two weeks in 88 patients with mMCC who have received at least one previous chemotherapy regimen. The primary endpoint is confirmed ORR, as determined by an independent review committee (IRC). An analysis was performed using data from 80 patients with metastatic MCC who have received at least one infusion of avelumab as of August 5, 2015. Of these 80 patients, there were 68 patients with a minimum duration of follow-up of six weeks, 55 patients with at least twelve weeks, and 28 patients with at least 24 weeks of follow-up. The following table copied from EMD Serono's briefing materials summarizes the IRC confirmed ORR by duration and follow-up.

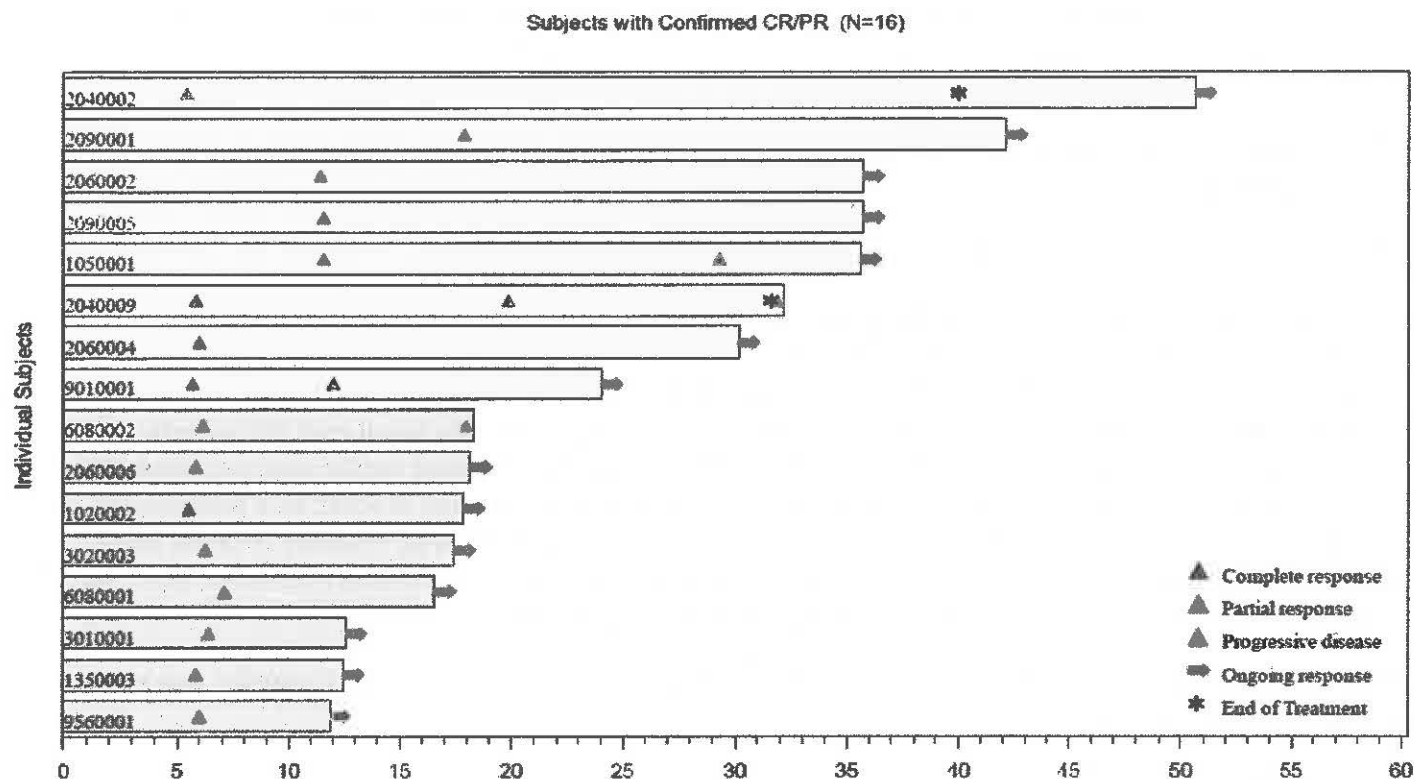
Table 3: IRC Confirmed ORR by Duration of Follow-Up

	Avelumab (n=68) ≥ 6 Weeks Follow-up	Avelumab (n=55) ≥ 12 Weeks Follow-up	Avelumab (n=28) ≥ 24 Weeks Follow-up
ORR (CR+PR), n(%); (95% CI)	16 (23.5); (14.1, 35.4)	16 (29.1); (17.6, 42.9)	8 (28.6); (13.2, 48.7)
Complete Response	5 (7.4)	5 (9.1)	4 (14.3)
Partial Response	11 (16.2)	11 (20.0)	4 (14.3)
Stable Disease	7 (10.3)	6 (10.9)	4 (14.3)
Progressive Disease	23 (33.8)*	22 (40.0)	11 (39.3)
Not Evaluable**	22 (32.4)	11 (20.0)	5 (17.9)

EMD Serono states that the focus of the BTDR will be the response and duration of response data from the 28 patients who have had at least 24 weeks of follow-up on Study EMR10070-003. The ORR for this subgroup was 29% [Confidence Interval (CI):13, 49]. Of the eight patients who experienced an objective response, four patients had a complete response (CR) and four experienced a partial response (PR). The range of the duration of response (DOR) from the onset of confirmed response for the eight responders at the time of data cutoff was 4.2 to 10.3 months. The median duration of response was not reached, and seven patients had ongoing responses ranging six months or longer. One patient who experienced a PR at 6 weeks followed by a CR at approximately 20 weeks developed progressive disease at Week 32. EMD Serono additionally notes that three of the patients who initially experienced a PR then had a CR following 6, 14 and 18 weeks of follow-up. The duration of response data is summarized in the swimmer's plot copied from the BTDR briefing document below. The yellow bars represent the responding patients with at least 24 weeks of follow-up.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Figure 2: Time to and Duration of Response Determined by IRC (Confirmed) for Responders with At Least 6 Weeks of Follow-up



b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

DOP2 considers the objective response and duration of response data from patients with metastatic MCC refractory to at least one line of prior chemotherapy treated with avelumab in Study EMR 100070-003 to be preliminary evidence of a substantial improvement over salvage chemotherapy treatment options.

The summary safety data provided in the BTDR briefing materials and in the Investigator's Brochure for avelumab were also reviewed. Eighty patients with metastatic MCC have received at least one infusion during Study EMR 100070-003. The median duration of exposure was ten weeks (range: 2-46 weeks). The most common adverse events (AEs) were fatigue, nausea, infusion-related reactions, rash, chills, asthenia, decreased appetite, and diarrhea. There have been no grade 4 or 5 AEs. Four percent (n=3) of patients had grade 3 AEs which were

anemia, transaminase elevation and ascites. One patient required discontinuation of treatment for grade 3 transaminase elevation. Given the mechanism of action, immune-related AEs (irAEs) are anticipated. Five percent (n=4) of patients experienced an irAE. These were grade 1 or 2 in severity and included two cases of hypothyroidism and two cases of thrombocytopenia. DOP2 considers this safety profile to be relatively favorable compared to cytotoxic chemotherapy.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

There are no systemic therapies approved for patients with metastatic MCC. Although known to be a chemosensitive disease, responses to chemotherapy are not durable and have not been shown to improve overall survival. DOP2 considers the effect size on response rate of 29% together with the durability of responses (ranging from 4.2 to 10.3 months) in patients with metastatic MCC who have progressed following at least one line of prior chemotherapy demonstrated so far in Study EMR1000-003 to be preliminary evidence of a substantial improvement over alternative treatment options which include off-label use of salvage chemotherapy regimens, none of which have demonstrated evidence of durable responses or improvements in survival. DOP2 has also considered the relatively favorable safety profile of avelumab as compared to further cytotoxic chemotherapy for patients with refractory metastatic MCC, the majority of whom are over 70 years of age and may have baseline comorbidities.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

DOP2 has had multiple teleconferences with EMD Serono to discuss the design of Study EMR100070-003 which is intended to support an application for accelerated approval. DOP2 has additionally provided written advice to EMD Serono regarding the design and endpoints of the planned confirmatory Study EMR 100070-006. DOP2 will continue to communicate with EMD Serono and provide regulatory guidance to facilitate the development program for avelumab in metastatic Merkel cell carcinoma.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

1. Becker, J.C., Merkel cell carcinoma. *Ann Oncol*, 2010. 21 Suppl 7: p.81-5.
2. Porceddu, S.V., et. al., Nonmelanoma Cutaneous Head and Neck Cancer and Merkel Cell Carcinoma: Current Concepts, Advances, and Controversies. *J Clin Oncol*, 2015. 33(29): p. 3338-45.
3. Iyer, J.G., et al., Response rate and durability of chemotherapy for metastatic Merkel cell carcinoma among 62 patients. *J Clin Oncol*, 2014 ASCO Annual Meeting abstracts. 32 (15): abstract 9091.
4. NCCN Clinical Practice Guidelines in Oncology, Merkel Cell Carcinoma, Version 2.2015.
5. Akhtar, S. et. al., Merkel cell carcinoma: report of 10 cases and review of the literature. *J Am Acad Dermatol*, 2000. 43(5 Pt 1): p. 755-67.
6. Voog, E., et al., Chemotherapy for patients with locally advanced or metastatic Merkel cell carcinoma. *Cancer*, 1999. 85(12): p. 2589-95.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

4-6-15/M. Raggio

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/s/

SANDRA J BENTON
11/18/2015

PATRICIA KEEGAN
11/19/2015



IND 119394

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

EMD Serono, Inc.
Attention: Darlene Noci, A.L.M., R.A.C.
Senior Director, Global Regulatory Strategy Lead, Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Noci:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for avelumab (MSB0010718C).

We also refer to your September 18, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that avelumab for the treatment of patients with metastatic Merkel cell carcinoma (mMCC) who have progressed after at least one previous chemotherapy regimen, meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of avelumab for the treatment of patients with mMCC to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting². Please refer to the *Guidance for Industry: Formal Meetings*

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

*between FDA or Sponsors and Applicants*³ for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project Manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for avelumab for the treatment of patients with mMCC who have progressed after at least one previous chemotherapy regimen is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Anuja Patel, Senior Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
11/17/2015

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761049

LATE-CYCLE MEETING MINUTES

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 Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Bavencio (avelumab) injection, for intravenous use, 200 mg/10 mL (20 mg/mL) solution in single-dose vial.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on February 27, 2017.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

Suzanne Demko
Cross Discipline Team Lead (CDTL)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: February 27, 2017; 3:00 PM- 4:00 PM
Meeting Location: Not Applicable; teleconference

Application Number: BLA761049
Product Name: Bavencio (avelumab) injection, for intravenous use; 200 mg/10 mL (20 mg/mL) solution in single-dose vial
Applicant Name: EMD Serono, Inc.

Meeting Chair: Suzanne Demko
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Patricia Keegan, Director, Division of Oncology Products (DOP2), OHOP
Suzanne Demko, Cross Discipline Team Leader, DOP2/ OHOP
Denise Casey, Clinical Reviewer, DOP 2/ OHOP
Idara Udoh, Senior Regulatory Project Manager, DOP2/ OHOP
Whitney Helms, Nonclinical Team Leader, Division of Hematology/Oncology Toxicology (DHOT) Products

EMD SERONO ATTENDEES

Virginia Pappalardo, Global Regulatory Lead, Global Regulatory Affairs, EMD Serono
Jennifer Stevens, Global Regulatory Affairs Program Lead, EMD Serono
Philippe Serrano, Global Head, Regulatory Affairs Oncology, Merck KGaA
Jacques Mascaro, Senior Vice President, Head of Global Regulatory Affairs and R&D Quality, Merck KGaA
Achta Paraiso, Manager, Biotech Regulatory CMC Unit, Merck KGaA
Kevin Chin, Executive Medical Director, Immuno-Oncology, Global Clinical Development, EMD Serono
Meliessa Hennessy, Global Clinical Development
Alise Reicin, Global Clinical Development
Anja von Heydebreck, Global Statistics, Merck KGaA
Berend Neuteboom, Senior Global Early Development Lead, EMD Serono
Haiqing (Isaac) Dai, Director, Clinical Pharmacology, EMD Serono
Laurie Strawn, Global Regulatory, Pfizer
Cecile Lloret, Global Project Management
Gülseren Güzel, Global Drug Safety, Merck KGaA
Glen Andrews, Pfizer Immuno-Oncology Asset Team Leader
Kamal Shah, Global Drug Safety
Christian Wrehlke, GRA Labeling

BACKGROUND

BLA 761049 was submitted on September 23, 2016 for Bavencio (avelumab) injection.

Proposed indication(s): Treatment of Merkel cell carcinoma

PDUFA goal date: May 23, 2017

FDA issued a Background Package in preparation for this meeting on February 17, 2017.

DISCUSSION

1. Introductory Comments (RPM/CDTL)

Welcome, Introductions

REVIEW ISSUES

2. Discussion of Additional Applicant Data (FDA/Applicant)

Discussion: FDA informed EMD Serono that there were no additional applicant data to address, excluding labeling negotiations.

Postmarketing Requirements (PMR)/Postmarketing Commitments (PMC)

PMR

Clinical

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 to be followed for a minimum of 12 months to establish the objective response rate and characterize the durability of response. Overall survival will be followed to maturity until at least 70% of patients have died, or for an additional two years beyond the primary data analysis cut-off, to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided.

Discussion: No discussion occurred.

PMC

Clinical Pharmacology

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 assay and the neutralizing assay as requested in PMC 1) 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 ADA response should 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 cut-point.

Discussion: No discussion occurred.

CMC

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.

Discussion: No discussion occurred.

CMC Microbiology

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.

Discussion: No discussion occurred.

Nonclinical

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 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 an evaluation of cytokine production by T cells at appropriate time-points.

Discussion: EMD Serono acknowledged FDA's request for this animal study and agreed to the proposed schedule milestones.

3. Major Labeling Issues – TBD

Discussion: FDA stated there were no major labeling issues. The indication statement is still under discussion, and an answer regarding the broader proposed indication is forthcoming.

Section 13.2 has been added to be consistent with the labeling of product of similar drug class.

Many prescribers have informed FDA that multiple indication labels are confusing when using study numbers, so FDA is going in the direction of naming trials. FDA requested that EMD Serono reconsider this during the next round of labeling negotiations.

FDA addressed the issue regarding including myocarditis in the label (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. FDA responded that where there are data, such cases need to be investigated and considered in the label; however, if there are no data, including myocarditis in a listing of "other" immune-related toxicities may be more appropriate.

4. Review Plans

Two meetings to discuss the proposed package insert labeling are tentatively scheduled for March 1, 2017 and March 6, 2017. Additional meetings will be scheduled as needed. If these timelines change, we will communicate updates to you during the course of review.

Discussion: No discussion occurred. See FDA response to agenda item #3.

5. Wrap-up and Action Items

Discussion: FDA stated that the draft package insert and Medication Guide will be provided with additional FDA revisions by the end of the week. A teleconference set aside for continued labeling negotiations is scheduled March 6, 2017; EMD Serono's response to the revised package insert and Medication Guide is due prior to the teleconference.

EMD Serono concluded by inquiring how rapidly they should be turning around the label and other outstanding items.

FDA stated that the application has not yet been fully reviewed by the Signatory Authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the final regulatory decision or date for acting on the application were not addressed.

The meeting concluded.

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/s/

SUZANNE G DEMKO
03/21/2017



BLA 761049

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

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 Biologic License Application (BLA) submitted under the Public Health Service Act for Bavencio (avelumab) injection, for intravenous use; 200 mg/10 mL (20 mg/mL) solution in single-dose vial.

We also refer to the Late-Cycle Meeting (LCM) scheduled for February 27, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at Idara.Udoh@fda.hhs.gov, no later than February 23, 2017.

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

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: February 27, 2017; 1:00 PM- 2:00 PM
Meeting Location: Teleconference

Application Number: BLA761049
Product Name: Bavencio (avelumab) injection, for intravenous use; 200 mg/10 mL (20 mg/mL) solution in single-dose vial
Indication: Treatment of patients with metastatic Merkel cell carcinoma
Applicant Name: EMD Serono, Inc.

FDA ATTENDEES (tentative)

Richard Pazdur, Director, Office of Hematology and Oncology Products (OHOP)
Amy McKee, Acting Deputy Office Director, OHOP
Patricia Keegan, Director, Division of Oncology Products (DOP2), OHOP
Suzanne Demko, Clinical Discipline Team Leader, DOP2/ OHOP
Denise Casey, Clinical Reviewer, DOP 2/ OHOP
Idara Udoh, Senior Regulatory Project Manager, DOP2/ OHOP

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date, and none are anticipated.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date, and none are anticipated.

LCM AGENDA

1. Introductory Comments (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

REVIEW ISSUES

2. Additional Applicant Data (FDA/Applicant)

Postmarketing Requirements (PMR)/Postmarketing Commitments (PMC)

PMR

Clinical

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 to be followed for a minimum of 12 months to establish the objective response rate and characterize the durability of response. Overall survival will be followed to maturity until at least 70% of patients have died, or for an additional two years beyond the primary data analysis cut-off, to characterize effects on survival. An analysis of overall survival compared to historical control data will be provided.

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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 cut-point.

CMC

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3. Major Labeling Issues – TBD

4. Review Plans

Two meetings to discuss the proposed package insert labeling are tentatively scheduled for March 1, 2017 and March 6, 2017. Additional meetings will be scheduled as needed. If these timelines change, we will communicate updates to you during the course of review.

5. Wrap-up and Action Items

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/s/

IDARA UDOH
02/17/2017