

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761078Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

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

NDA/BLA#: BLA# 761078 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: DOP 1 PDUFA Goal Date: 08/27/17 Stamp Date: 12/27/2016

Proprietary Name: Bavencio

Established/Generic Name: avelumab

Dosage Form: Injection

Applicant/Sponsor: EMD Serono, Inc.

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

- (1) N/A
(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: locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy

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 | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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 † |
|---|---------------------------|---------------|---------------|------------------------------|---|---|---------------------------|
| | | | | Ready for Approval in Adults | Need Additional Adult Safety or Efficacy Data | Other Appropriate Reason (specify below)* | Received |
| Population | | minimum | maximum | | | | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Populations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 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?. | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

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 |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | 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 (cderpmhs@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? |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

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)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

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

Q2: 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 | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

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 Section 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 some or all 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 | |
| <input type="checkbox"/> Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| <input type="checkbox"/> All Pediatric Populations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 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? | |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | Yes <input type="checkbox"/> | No <input type="checkbox"/> |

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 |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. |
| <input type="checkbox"/> | 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 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? |
| <input type="checkbox"/> | Neonate | __ wk. __ mo. | __ wk. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | Other | __ yr. __ mo. | __ yr. __ mo. | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | All Pediatric Subpopulations | 0 yr. 0 mo. | 16 yr. 11 mo. | <input type="checkbox"/> | <input type="checkbox"/> |

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(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/

KIM J ROBERTSON
02/08/2017



Geoffrey Kim, M.D.
Director Division of Oncology Products I
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
US Food and Drug Administration
Central Document Room 5901-B
Ammendale Road Beltsville, MD 20705-1266

Re: Debarment Certification Letter for Avelumab BLA 761078

Dear Dr. Kim,

EMD Serono Research and Development Institute, Inc. (EMD Serono R&D) hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application, BLA 761078.

Sincerely,

A handwritten signature in cursive script that reads "Alise Reicin".

Alise Reicin, MD
Head, Global Clinical Development

A handwritten date in cursive script that reads "Dec 8, 2016".

Date

EMD Serono Research and Development Institute, Inc.
45A Middlesex Turnpike, Billerica, MA 01821 United States
Phone: 978-294-1293

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|----------------------|---|
| BLA # 761078 | BLA Supplement # N/A | If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i> |
| Proprietary Name: Bavencio™ Established/Proper Name: (avelumab) Dosage Form: 20 mg/mL, 10 mg/kg | | Applicant: EMD Serono, Inc. Agent for Applicant (if applicable): N/A |
| RPM: Kim J. Robertson | | Division: DOP1 |
| NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) | | <p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> 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) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> <p>Date of check: _____</p> <p><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></p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>August 27, 2017</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> | | <input checked="" type="checkbox"/> 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 _____ | | <input checked="" type="checkbox"/> Received April 7, 2017 |
| ❖ 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): N/A
 (confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> 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) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| ❖ Public communications (approvals only) | |
| • Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| • Indicate what types (if any) of information were issued | <input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Burst |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | <input type="checkbox"/> Verified <input type="checkbox"/> 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) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees | <input checked="" type="checkbox"/> Included |

| Action Letters | |
|---|--|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i> | Action(s) and date(s) May 9, 2017 |
| Labeling | |
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i> | |
| <ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input checked="" type="checkbox"/> Included April 27, 2017 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included December 27, 2016 |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i> | <input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input checked="" type="checkbox"/> Included April 27, 2017 |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included December 27, 2016 |
| ❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i> | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | <input checked="" type="checkbox"/> Included April 7, 2017 |
| ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> | March 10, 2017 March 2, 2017 |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i> | RPM: <input type="checkbox"/> None February 24, 2017 DMEPA: <input type="checkbox"/> None April 18, 2017 DMPP/PLT (DRISK): <input type="checkbox"/> None April 15, 2017 OPDP: <input type="checkbox"/> None April 13, 2017 SEALD: <input checked="" type="checkbox"/> None N/A CSS: <input checked="" type="checkbox"/> None N/A Product Quality <input type="checkbox"/> None April 3, 2017 Other: <input type="checkbox"/> None |
| Administrative / Regulatory Documents | |
| ❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i> | February 24, 2017 |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | <input type="checkbox"/> Not a (b)(2) |
| ❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i> | <input type="checkbox"/> Completed |

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

| | |
|---|--|
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ 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>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input checked="" type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>March 22, 2017</u> If PeRC review not necessary, explain: <u>N/A</u> | |
| ❖ Breakthrough Therapy Designation | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) | N/A |
| <ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) | N/A |
| <ul style="list-style-type: none"> • 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>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p> | 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>) | May 3, 2017; May 2, 2017(4); May 1, 2017; April 26, 2017; April 25, 2017(2); April 24, 2017; April 21, 2017; April 13, 2017; April 7, 2017(4); April 6, 2017(3); April 3, 2017; March 28, 2017(2); March 22, 2017(2); March 21, 2017; March 17, 2017(2); March 16, 2017(3); March 14, 2017(3); March 10, 2017; March 8, 2017; March 7, 2017; March 6, 2017(7); March 3, 2017; March 2, 2017(2); March 1, 2017; February 27, 2017(2); February 24, 2017; February 23, 2017(2); February 22, 2017; February 21, 2017; January 25, 2017(4); January 17, 2017; January 12, 2017(2); January 11, 2017; January 4, 2017 |
| ❖ 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) | March 9, 2017 |

| | |
|--|---|
| ❖ Minutes of Meetings | October 14, 2015 |
| • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> N/A or no mtg |
| • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg October 6, 2016 |
| • EOP2 meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> No mtg |
| • Mid-cycle Communication (<i>indicate date of mtg</i>) | <input type="checkbox"/> N/A March 9, 2017 |
| • Late-cycle Meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> N/A April 7, 2017 |
| • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) | Pre IND: September 30, 2015 |
| ❖ Advisory Committee Meeting(s) | <input checked="" type="checkbox"/> No AC meeting |
| • Date(s) of Meeting(s) | N/A |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None See uni-review under clinical tab dated May 8, 2017 |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input type="checkbox"/> None See uni-review under clinical tab dated May 8, 2017 |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input type="checkbox"/> None 1PMR; 1PMC |
| Clinical | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review Uni-Review dated: May 8, 2017 |
| • Clinical review(s) (<i>indicate date for each review</i>) | Uni-Review dated: May 8, 2017 |
| • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) | See Uni-Review dated May 8, 2017 |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵ | <input checked="" type="checkbox"/> None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> N/A |
| ❖ Risk Management | |
| • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) | N/A |
| • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) | |
| • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) | <input type="checkbox"/> None |
| ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) | <input type="checkbox"/> None requested April 17, 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).

| | |
|---|--|
| Clinical Microbiology <input checked="" type="checkbox"/> None | |
| ❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review |
| Statistical Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review |
| Statistical Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None See uni-review dated: May 8, 2017 |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> None See uni-review dated: May 8, 2017. See also Clinpharm Memo dated: April 27, 2017 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>) | <input checked="" type="checkbox"/> None requested |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| • Supervisory Review(s) (<i>indicate date for each review</i>) | <input type="checkbox"/> No separate review |
| • Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) | <input type="checkbox"/> None See uni-review dated: May 8, 2017. |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) | <input type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input type="checkbox"/> None Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>) | <input type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews ⁶ | |
| • Tertiary review (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> None |
| • Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>) | <input type="checkbox"/> None April 3, 2017 |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>) | <input type="checkbox"/> None April 3, 2017 |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>) | <input checked="" type="checkbox"/> None |

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

| | |
|---|---|
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | April 3, 2017 |
| <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | N/A |
| <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | April 3, 2017 |
| ❖ Facilities Review/Inspection | |
| <input checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>) | <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |

| Day of Approval Activities | |
|---|--|
| <ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) |
| <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager | <input type="checkbox"/> Done <i>(Send email to CDER OND IO)</i> |
| <ul style="list-style-type: none"> ❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ 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 | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate | <input type="checkbox"/> Done |
| <ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS | <input type="checkbox"/> Done |

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, May 02, 2017 4:48 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078: Request for Modification to Label
Attachments: 02May17 BLA 761078 (avelumab) USPI wFDA Edits.docx

Importance: High

Dear Jennifer:

Please see the attached Word .doc, as it is EMD's avelumab USPI with additional FDA Edits. Please review and return the label to us by **Thursday, May 4, 2017, 11:00am EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Monday, May 01, 2017 7:07 PM
To: Robertson, Kim
Subject: BLA 761078: Request for Modification to Label
Importance: High

Dear Kim,

Today we saw the announcement of FDA's approval of IMFINZI (durvalumab). In reviewing the label, we noted that FDA had permitted ongoing response information in the text. Please see p. 17 of the approved label for durvalumab which reads:

"Among the total 31 responding patients, 14 patients (45%) had ongoing responses of 6 months or longer and five patients (16%) had ongoing responses of 12 months or longer."

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf

In the label FDA sent to EMD related to Bavencio (avelumab) on April 21, 2017, FDA proposed language related to ongoing response (lines 641- 644 on page 21 of the attached). In response to some proposed edits by EMD, FDA provided another label on April 26, 2017 wherein FDA removed all reference to ongoing response with the following comment from Dr. Maher:

“To Applicant:

To avoid confusion, we have removed

(b) (4)

(see attached at page 21).

By including this information in the IMFINZI label, it appears that FDA has modified its position on including the ongoing response information for PD-1/PD-L1 labels for the UC indication since the April 26th comment from Dr. Maher . In the interest of equitable comparability, we respectfully request that FDA reinstate its suggested language from the April 21, 2017 draft into the Bavencio label which reads:

(b) (4)

We would be available for a brief call should FDA wish to discuss this matter.

Thank you and best regards,

Jennifer

Jennifer L. Stevens, J.D

Global Program Regulatory Lead; Immuno-Oncology
Biopharma | Global Research & Development | Global Regulatory Oncology

EMD Serono

A business of Merck KGaA, Darmstadt, Germany

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Washington, D.C. 20004 | USA

Office: +1 202 393 4736 | Mobile: (b) (6) | Fax: 202 393 7464

E-mail: jennifer.stevens@emdserono.com

www.emdserono.com

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25 Page(s) have 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/

KIM J ROBERTSON
05/02/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, May 02, 2017 11:17 AM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078: Request for Modification to Label

Dear Jennifer:

I have forwarded EMD's modification request to the reviewing clinical reviewers and I will notify you whether or not the clinical reviewers will need a t-con with EMD.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Monday, May 01, 2017 7:07 PM
To: Robertson, Kim
Subject: BLA 761078: Request for Modification to Label
Importance: High

Dear Kim,

Today we saw the announcement of FDA's approval of IMFINZI (durvalumab). In reviewing the label, we noted that FDA had permitted ongoing response information in the text. Please see p. 17 of the approved label for durvalumab which reads:

"Among the total 31 responding patients, 14 patients (45%) had ongoing responses of 6 months or longer and five patients (16%) had ongoing responses of 12 months or longer."

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf

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"To Applicant:

To avoid confusion, we have removed

(b) (4)

(see attached at page 21).

By including this information in the IMFINZI label, it appears that FDA has modified its position on including the ongoing response information for PD-1/PD-L1 labels for the UC indication since the April 26th comment from Dr. Maher . In the interest of equitable comparability, we respectfully request that FDA reinstate its suggested language from the April 21, 2017 draft into the Bavencio label which reads:

(b) (4)

We would be available for a brief call should FDA wish to discuss this matter.

Thank you and best regards,

Jennifer

Jennifer L. Stevens, J.D

Global Program Regulatory Lead; Immuno-Oncology
Biopharma | Global Research & Development | Global Regulatory Oncology

EMD Serono

A business of Merck KGaA, Darmstadt, Germany

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Washington, D.C. 20004 | USA
Office: +1 202 393 4736 | Mobile: (b) (6) | Fax: 202 393 7464
E-mail: jennifer.stevens@emdserono.com
www.emdserono.com

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/s/

KIM J ROBERTSON
05/02/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, May 02, 2017 11:18 AM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab

Thank you Jennifer.
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Monday, May 01, 2017 7:08 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab

Dear Kim,

The requested list is attached. Regards, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, May 01, 2017 3:41 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab

Dear Jennifer:

Would you be able to provide me with the names of your key people that participated in EMD Serono's April 7, 2017 Late Cycle Teleconference Meeting?

Thank you,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1

Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
05/02/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, May 02, 2017 4:36 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab--Clinical Information Request

Thank you for this Jennifer.
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Tuesday, May 02, 2017 11:33 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab--Clinical Information Request

Dear Kim,

Attached is a courtesy copy of EMD Serono's response to the IR below. This response is being submitted to the BLA today. Regards, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, May 01, 2017 11:51 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab--Clinical Information Request
Importance: High

Dear Jennifer:

Relative to EMD Serono's BLA for avelumab, my clinical reviewers have the following request for information:

CLINICAL INFORMATION REQUEST:

The existing PI states that patients should be pre-medicated prior to the first 4 infusions. Our understanding was that patients in the UC cohort were pre-medicated prior to each infusion. While we acknowledge that the majority of infusion-related reactions happened during the early infusions, we are concerned that the incidence of infusion reactions

in the UC cohort without pre-medications during later infusions is unknown. Please provide your rationale and data to support this statement in your package insert.

Please provide us with a response to this inquiry by **Tuesday, May 2, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

**Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration**

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
05/02/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, May 01, 2017 11:51 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--Clinical Information Request
Importance: High

Dear Jennifer:

Relative to EMD Serono's BLA for avelumab, my clinical reviewers have the following request for information:

CLINICAL INFORMATION REQUEST:

The existing PI states that patients should be pre-medicated prior to the first 4 infusions. Our understanding was that patients in the UC cohort were pre-medicated prior to each infusion. While we acknowledge that the majority of infusion-related reactions happened during the early infusions, we are concerned that the incidence of infusion reactions in the UC cohort without pre-medications during later infusions is unknown. Please provide your rationale and data to support this statement in your package insert.

Please provide us with a response to this inquiry by **Tuesday, May 2, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
05/01/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, April 26, 2017 5:23 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab USPI wFDA Edits and Comments
Attachments: 26April17 BLA 761078 (avelumab) USPI wFDA Edits Comments.docx
Importance: High

Dear Jennifer:

Please see the attached Word .doc, as it is EMD Serono's avelumab USPI with FDA Edits and Comments. Please review with your colleagues and provide us with a return label, with either EMD's concurrence and acceptance of our tracked changes, or any additional edits/comments EMD might have by **Friday, April 28, 2017, 12:00Noon, EST.**

Please note-- extensive labeling negotiations will delay your action. We consider the package insert that we are sending back to you to be *very* close to the final version.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/26/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, April 25, 2017 1:37 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab-- Clinical Information Request

Thank you very much Jennifer.
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Tuesday, April 25, 2017 6:12 AM
To: Robertson, Kim
Subject: Re: BLA 761078; avelumab-- Clinical Information Request

Hi Kim- I acknowledge your request. We will respond by tomorrow as requested. Regards, Jennifer

Sent from my iPhone

On Apr 24, 2017, at 5:10 PM, Robertson, Kim <Kim.Robertson@fda.hhs.gov> wrote:

Dear Jennifer:

As we continue our review of EMD Serono's BLA for avelumab, the clinical reviewer has the following requests for information:

CLINICAL INFORMATION REQUEST:

1. How many patients in the urothelial cohorts of Study 001 received infusions of avelumab using only process A, how many received both process A and B, and how many received only process B?
2. How many infusions used process A and how many process B?
3. Please provide a breakdown of the infusion-related reactions by which product, process A or B, was used.

We urgently need you to provide responses to address these queries by **Wednesday, April 26, 2017, 12Noon, EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

**Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration**
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/25/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, April 25, 2017 1:58 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab-- Clinical Information Request

Thank you for this information Jennifer. I will forward it to the requesting reviewer at once.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Tuesday, April 25, 2017 1:44 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab-- Clinical Information Request

Dear Kim – Attached is a courtesy copy of EMD Serono, Inc.'s response to the FDA IR below. This response will be submitted to the BLA tomorrow.

Regards, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, April 24, 2017 4:52 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab-- Clinical Information Request
Importance: High

Dear Jennifer:

As we continue our review of EMD Serono's BLA for avelumab, the clinical reviewer has the following requests for information:

CLINICAL INFORMATION REQUEST:

1. How many patients in the urothelial cohorts of Study 001 received infusions of avelumab using only process A, how many received both process A and B, and how many received only process B?
2. How many infusions used process A and how many process B?
3. Please provide a breakdown of the infusion-related reactions by which product, process A or B, was used.

We urgently need you to provide responses to address these queries by **Wednesday, April 26, 2017, 12Noon, EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/25/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, April 24, 2017 10:52 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab-- Clinical Information Request
Importance: High

Dear Jennifer:

As we continue our review of EMD Serono's BLA for avelumab, the clinical reviewer has the following requests for information:

CLINICAL INFORMATION REQUEST:

1. How many patients in the urothelial cohorts of Study 001 received infusions of avelumab using only process A, how many received both process A and B, and how many received only process B?
2. How many infusions used process A and how many process B?
3. Please provide a breakdown of the infusion-related reactions by which product, process A or B, was used.

We urgently need you to provide responses to address these queries by **Wednesday, April 26, 2017, 12Noon, EST.**

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
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Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/24/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, April 21, 2017 1:24 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--USPI with FDA Edits and Comments
Attachments: 21April17 BLA 761078 (avelumab) USPI wFDA Edits and Comments.docx
Importance: High

Dear Jennifer:

Please see the attached Word .doc, as it is EMD Serono's avelumab USPI with FDA Edits and Comments. Please review with your colleagues and provide us with a return label, with either EMD's concurrence and acceptance of our tracked changes, or any additional edits/comments EMD might have, by **Tuesday, April 25, 2017, 2:00pm EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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KIM J ROBERTSON
04/21/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, April 13, 2017 6:25 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Pharmacology PMC
Importance: High

Dear Jennifer:

Please review and either agree with, or provide us with your proposed milestone date relative to the following clinical pharmacology PMC:

PMC Description: Submit the final report and data for safety and efficacy of the ongoing clinical trial Set # 3201 EMR100070-005 entitled “A Phase III, open-label, multicenter trial of avelumab (MSB0010718C) versus platinum-based doublet as a first-line treatment of recurrent or Stage IV PD-L1+ non–small-cell lung cancer”, including results of the exposure-response analysis.

PMC Schedule Milestone: Final Report Submission 06/30/2019

Please respond by **Monday, April 17, 2017.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/13/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, April 13, 2017 6:19 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab--Update to Clinical PMR

Importance: High

Dear Jennifer:

Our safety colleagues who focus on PMR/PMC milestones have made a few minor revisions to the Clinical PMR that I initially sent forth that we need EMD to review and agree to revise:

PMR Description:

#3201-1 Conduct "Javelin Bladder 100: A Phase 3, Multicenter, Multinational, Randomized, Open-label Parallel-arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone as a Maintenance Treatment in patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-line Platinum-containing Chemotherapy" and provide a final report, datasets, and revised labeling.

PMR Schedule Milestone:

| | |
|--------------------------|----------------|
| Study/Trial Completion: | <u>09/2020</u> |
| Final Report Submission: | <u>03/2021</u> |

Also, in your response, we noted you added the following: (b) (4), therefore, we will disregard that inclusion. The date for the Final Report ("FR") was revised to 03/2021, because applicants have 6 months to submit their "FR", upon the completion of the trial.

Please review and provide us with an updated response by **Monday, April 17th, 2017.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Tuesday, April 11, 2017 4:19 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab--Clinical PMR

Dear Kim – Attached is our response to the milestone request below. It is being submitted to the BLA today. Regards,
Jennifer

From: Robertson, Kim [mailto:Kim.Robertson@fda.hhs.gov]
Sent: Friday, April 07, 2017 6:12 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab--Clinical PMR
Importance: High

Dear Jennifer:

Please provide us with milestone dates relative to the following clinical PMR:

PMR Description:

#3201-1 Conduct “Javelin Bladder 100: A Phase 3, Multicenter, Multinational, Randomized, Open-label Parallel-arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone as a Maintenance Treatment in patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-line Platinum-containing Chemotherapy” and provide a final report, datasets, and revised labeling.

PMR Schedule Milestone:

| | |
|--------------------------|----------------|
| Study/Trial Completion: | <u>MM/YYYY</u> |
| Final Report Submission: | <u>MM/YYYY</u> |

Please provide your milestone responses by **Tuesday, April 11, 2017.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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KIM J ROBERTSON
04/13/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, April 07, 2017 6:11 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--Clinical PMR
Importance: High

Dear Jennifer:

Please provide us with milestone dates relative to the following clinical PMR:

PMR Description:

#3201-1 Conduct "Javelin Bladder 100: A Phase 3, Multicenter, Multinational, Randomized, Open-label Parallel-arm Study of Avelumab Plus Best Supportive Care Versus Best Supportive Care Alone as a Maintenance Treatment in patients with Locally Advanced or Metastatic Urothelial Cancer Whose Disease Did Not Progress After Completion of First-line Platinum-containing Chemotherapy" and provide a final report, datasets, and revised labeling.

PMR Schedule Milestone:

| | |
|--------------------------|----------------|
| Study/Trial Completion: | <u>MM/YYYY</u> |
| Final Report Submission: | <u>MM/YYYY</u> |

Please provide your milestone responses by **Tuesday, April 11, 2017.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
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U.S. Food and Drug Administration
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kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/07/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, April 07, 2017 5:46 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab --USPI with FDA Edits/Comments
Attachments: 07April17 Approved Avelumab USPI and MG Updated with UC Info for DOP1.docx
Importance: High

Dear Jennifer:

Please see the attached Word .doc, as it is EMD Serono's avelumab USPI with FDA Edits and Comments. Please review and send us a return label with EMD's concurrence and/or comments by **Thursday, April 13, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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kim.robertson@fda.hhs.gov



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KIM J ROBERTSON
04/07/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, April 07, 2017 1:29 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab--- Follow-Up re: Carton/Container Labeling

Thank you Jennifer. I will look for the official submission of the final, approved carton and container labeling in DOP1's BLA number today.

~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Friday, April 07, 2017 1:26 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab--- Follow-Up re: Carton/Container Labeling

Dear Kim –

The final submission to the agreed container and carton labels was actually submitted to BLA 761049 today, in accordance with the action letter for the MCC indication – so these are the final, approved documents. We are now preparing these for submission to BLA 761078 - also today. Shortly, I will be able to send you the courtesy copy of these documents and the cover and 356h.

Regards, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, April 07, 2017 6:51 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab--- Follow-Up re: Carton/Container Labeling
Importance: High

Dear Jennifer:

Would you please provide me with the date that approved carton and container labeling was officially submitted to DOP1's BLA (#761078)? As I previously stated, we are also going to need the approved,

agreed upon version of the container label that was submitted to DOP2's BLA #761049 on **February 10, 2017** and carton labeling that was submitted to BLA #761049 on **February 24, 2017**.

Please advise.

Thank you,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

**Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration**
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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KIM J ROBERTSON
04/07/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, April 07, 2017 12:51 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--- Follow-Up re: Carton/Container Labeling
Importance: High

Dear Jennifer:

Would you please provide me with the date that approved carton and container labeling was officially submitted to DOP1's BLA (#761078)? As I previously stated, we are also going to need the approved, agreed upon version of the container label that was submitted to DOP2's BLA #761049 on **February 10, 2017** and carton labeling that was submitted to BLA #761049 on **February 24, 2017**.

Please advise.

Thank you,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/07/2017

From: [Fahnbulleh, Frances](#)
To: [Jennifer Stevens](#)
Cc: [Robertson, Kim](#); [Michael Bui](#)
Subject: RE: BLA 761078 Avelumab
Date: Thursday, April 06, 2017 5:00:39 PM

Dear Jennifer,

Thank you for the information provided below regarding your application. As you have noted, your 351(a) BLA is within the scope of our recently issued guidance for industry, Nonproprietary Naming of Biological Products. However, FDA issued the final guidance at a point in our review of your application that does not allow sufficient time for FDA to designate a proper name that includes a suffix as described in the guidance at this time. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your 351(a) BLA be approved during this review cycle.

I hope this answers your question. Please feel free to contact me if you have additional questions.

Respectfully,
Frances

Frances Fahnbulleh, RPh, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/WO22 , Rm#4404
Ph: 301-796-0942/Fax: 301-796-9835
Email: Frances.Fahnbulleh@fda.hhs.gov

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From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Thursday, April 06, 2017 11:39 AM
To: Fahnbulleh, Frances
Cc: Robertson, Kim; Michael Bui
Subject: RE: BLA 761078 Avelumab

Hello Frances –

Michael Bui reports to me and as I am out on vacation this week, I asked him to reach out to you to ensure that we are connecting on the current naming situation for avelumab. As you probably know, “Bavencio” was approved for avelumab by OHOP/DOP2 in association with the approval of avelumab for the treatment of metastatic Merkel cell carcinoma at the end of March (BLA 761049).

Currently, BLA 761078 is under review by DOP1 for avelumab for the treatment of metastatic or

locally advanced urothelial carcinoma following (b) (6) a platinum-based therapy. We are looking to market avelumab under a single label and a single trade name and will be looking to combine labels for approved indications (a number of other indications are currently under study by EMD Serono/Merck KGaA and/or its development partner, Pfizer).

One of the things I asked Mike to check on is the question of a suffix for avelumab, and the appropriate time for this submission. Our submission for BLA 761078 occurred at approximately the same time that the guidance was issued and therefore, we did not submit proposals at that time.

As our late cycle meeting with DOP1 is scheduled for tomorrow, I wanted Mike to touch base to ensure we were coordinating with your office and taking appropriate steps as needed.

Please feel free to respond to both Mike (cc'd above) and me (and Kim) so we all will be up to speed on appropriate action.

Regards, Jennifer

From: Fahnbulleh, Frances [<mailto:Frances.Fahnbulleh@fda.hhs.gov>]
Sent: Thursday, April 06, 2017 4:53 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Cc: Robertson, Kim <Kim.Robertson@fda.hhs.gov>
Subject: BLA 761078 Avelumab

Dear Jennifer,

Would you kindly provide me with the email address for Michael Bui? We've been playing phone tag, but his messages do not indicate the reason for his call. Would you have any idea what the call is regarding? I'm hoping we can communicate via email alternatively.

Kind Regards,
Frances

Frances Fahnbulleh, RPh, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/WO22, Rm#4404
Ph: 301-796-0942/Fax: 301-796-9835
Email: Frances.Fahnbulleh@fda.hhs.gov

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/s/

FRANCES G FAHNBULLEH
04/06/2017



BLA 761078

MID-CYCLE COMMUNICATION

EMD Serono, Inc.
Attention: Jennifer Stevens, JD
Global Regulatory Program Lead, Immuno-Oncology
One Technology Place
Rockland, MA 02370

Dear Ms. Stevens:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for Bavencio™ (avelumab), Intravenous, 20 mg/mL, 10 mg/kg.

We also refer to the teleconference between representatives of your firm and the FDA on March 9, 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 Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
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: Thursday, March 9, 2017, 11:00am-12:00pm, EST

Application Number: BLA 761078
Product Name: Bavencio™ (avelumab)
Indication: **Advanced or metastatic urothelial cancer (UC)**
Applicant Name: EMD Serono, Inc.

Meeting Chair: V. Ellen Maher, MD, Clinical Team Leader
Meeting Recorder: Kim J. Robertson, Regulatory Health Project Manager

FDA ATTENDEES

Geoffrey Kim, MD, Director, DOP1
Julia Beaver, MD, Supervisory Associate Director, DOP1
V. Ellen Maher, MD, Cross Discipline Team Leader, DOP1
Chana Weinstock, MD, Clinical Reviewer, DOP1
Nan Zheng, PhD, Clinical Pharmacology Reviewer DCP5
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP5
Joyce Cheng, PhD, Biometrics Reviewer, DBV
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Kim J. Robertson, Regulatory Health Project Manager, DOP1

EMD Serono, Inc Attendees:

Kevin Chin, MD, Vice President, Immuno-Oncology, EMD Serono
Galit Rosen, MD, Medical Director, Immuno-Oncology, EMD Serono
Marcis Bajars, MD, Medical Director, Immuno-Oncology, Merck KGaA
Jacques Mascaro, PhD, Sr. VP, Head of Global Regulatory Affairs & R&D Quality
Jennifer Stevens, JD, Global Regulatory Prog Lead, Immuno-Oncology, EMD Serono
Philippe Serrano, PhD, Head of Regulatory Immuno-Oncology/Oncology, EMD Serono
Junyuan Julia Xiong, MS, Assoc Director, Global Biostatistics, EMD Serono
Byron Robinson, PhD, JD, Avelumab Program Lead, EMD Serono
Helga Koch, PhD, Director, Global Drug Safety, Merck KGaA
Joleen White, PhD, Assoc Director, Global Early Development, EMD Serono
Yulia Vugmeyster, PhD, Clinical Pharmacologist, EMD Serono
Stefanie Fischer, Principal Clinical Data Sciences, Merck KGaA
Dagmar Kottig-Roth, PhD, Senior Data Standards and Governance Mgr, Merck KGaA
Michael Bui, DDS, JD, MPH, Director, Global Regulatory Affairs
Christian Wrehlke, PhD, MDRA, Assoc Director, Labeling
Shannon Dauksis, PharmD, PMP, R&D Project Manager
Laurie Strawn, PhD, Pfizer, Global Reg Portfolio Lead, Immuno-Onc/GU Malignancies

EMD Serono, Inc Attendees (cont.):

Andy Blake-Haskins, PharmD, Pfizer, Asset Team Lead

1.0 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.

2.0 SIGNIFICANT ISSUES

Clinical:

- The 13 week data will also be included in revised labeling.
- The Agency recommends that the Applicant optimize the dose of avelumab and notes that this may lead to a higher response rate in urothelial cancer. We plan to request a post-marketing commitment (PMC) to evaluate the efficacy and safety of BAVENCIO at a higher dose or a more frequent dose in patients with urothelial cancer (UC), depending on the results of the ongoing trial (EMR100070-005) in patients with non-small cell lung cancer (NSCLC). It is the applicant's choice however, to determine whether to start the dosing optimization trial after the results of the ongoing trial (EMR100070-005) are available.
- Clinical PMRs and PMCs have not yet been determined. There will be a PMR for the ongoing confirmatory study.

3.0 INFORMATION REQUESTS

- There are no outstanding information requests.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

All major safety concerns can be addressed through review of the submission and the responses to our information requests. A REMS will not be required.

5.0 ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

As we indicated during the Mid-Cycle Communication, we plan to act early on this application under an expedited review. The Late-Cycle Meeting between you and the review team is currently scheduled for Friday, April 7, 2017; 3:00pm- 3:30pm, Eastern Standard Time. We intend to send the briefing package to you approximately 2 days in advance of the meeting. If these timelines change, we will communicate updates to you during the course of review. You may choose to change this face-to-face meeting to a teleconference, or cancel the meeting altogether if you feel it is not needed given our continued and regular communications.

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/s/

VIRGINIA E MAHER
04/03/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, March 28, 2017 4:06 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

The clinical reviewer of EMD's BLA for avelumab has the following request for information:

CLINICAL INFORMATION:

- Please provide narratives for all patients who died within 30 days of treatment, regardless of reason for or attribution of deaths.

Please provide us with a response to address this IR by **Monday, April 3, 2017, 9:00am EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/28/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, March 28, 2017 3:21 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Additional Clinical Information Request -RESPONSE REQUESTED

No problem Jennifer.
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Tuesday, March 28, 2017 1:38 PM
To: Robertson, Kim
Subject: Re: BLA 761078; avelumab---Additional Clinical Information Request -RESPONSE REQUESTED

Thanks, Kim. We may well beat this date since more awaited data arrived today but I need to connect with my biomarker people first. Regards, Jennifer

Sent from my iPhone

On Mar 28, 2017, at 6:58 PM, Robertson, Kim <Kim.Robertson@fda.hhs.gov> wrote:

If April 3rd is the earliest you can provide the information, then we shall wait until April 3rd Jennifer.

Thank you,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

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Tel: 301-796-1441

kim.robertson@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL

From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Monday, March 27, 2017 4:51 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Additional Clinical Information Request -RESPONSE REQUESTED

Dear Kim,

With regard to the IR below, we had hoped to have the response to FDA today, however, it has taken longer to obtain some data than we originally anticipated and as a result, our response is delayed. We will have this response to FDA on or before Monday, April 3rd.

Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, March 22, 2017 9:38 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Additional Clinical Information Request -RESPONSE REQUESTED

Dear Jennifer:

Upon further review, the clinical reviewer double checked and you are correct in that the number should be **102/226** subjects for rescoring.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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Tel: 301-796-1441

kim.robertson@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL

From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Wednesday, March 22, 2017 11:57 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Additional Clinical Information Request -RESPONSE REQUESTED

Thank you Kim.

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, March 22, 2017 11:54 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Additional Clinical Information Request -RESPONSE REQUESTED

Dear Jennifer:

My clinical reviewers should be providing me with the clarification you seek today. I just wanted to touch base with you to let you know that we are still working on this.

~Kim

Kim J. Robertson

Regulatory Health Project Manager

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From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]

Sent: Tuesday, March 21, 2017 10:18 AM

To: Robertson, Kim

Subject: RE: BLA 761078; avelumab---Additional Clinical Information Request -RESPONSE REQUESTED

Importance: High

Dear Kim – We are working on the response to the request below and hope to have it to FDA by Friday or Monday latest. We do, however, need a clarification, please. FDA references 103/226 subjects for rescoring, however, the number we confirm is 102. Could you ask the Reviewer to double check that the 103 is correct – and if so, to point us to the basis for this figure?

It would be most helpful to have a response as soon as possible today. Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]

Sent: Tuesday, March 14, 2017 3:39 PM

To: Jennifer Stevens <jennifer.stevens@emdserono.com>

Subject: BLA 761078; avelumab---Additional Clinical Information Request

Dear Jennifer:

Relative to EMD's Original BLA for avelumab, the clinical reviewer has the following additional request for information:

CLINICAL INFORMATION REQUEST:

We refer to our March 1, 2017 information request and to your March 6, 2017 reply. Please provide the following additional, detailed information:

In the 226 patients who have been followed for at least 13 weeks and in the 161 patients who have been followed for at least 24 weeks:

1. Please state the initial PD-L1 score and the results of rescoring for the 103/226 and 101/161 patients who were rescored.

2. Please state the number of patients who were retested in each group (N = 226, N = 161) and the reason for retesting (e.g., < 150 cells on H&E, unacceptable control, technical factors such as tissue detachment from the slide or tissue folding on the slide, section tested for PD-L1 inconsistent with H&E screening slide, < 100 cells on PD-L1 stained section, and clinical requests. Please provide the USUBJID for the patients who were retested due to clinical request.
3. The number of unevaluable pts is higher than expected and could potentially impact the association between response rate and PD-L1 staining. Please state the number of patients in each group (N = 226, N = 161) who were un-evaluable due to: < 100 tumor cells in sample, tissue detachment from the slide, unacceptable control, decalcified tissue sample, and no sample received.

Please provide a timeline for your responses to our queries.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

**Division of Oncology Products 1
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KIM J ROBERTSON
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From: Robertson, Kim
Sent: Wednesday, March 22, 2017 4:41 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

Please see the following request for information from my clinical reviewer of EMD's BLA for avelumab:

CLINICAL INFORMATION REQUEST:

- In the ADSL analysis dataset submitted to BLA #761078 on January 23, 2017, there are an additional 24 deaths reported as having occurred in the 242 non-platinum naïve UC patients treated with avelumab that occurred after the DCO date of June 9, 2016. There are no death reasons reported for these patients. Please provide any additional information you may have relating to these deaths.

Please provide a response to this query no later than **Thursday, March 29, 2017, 3:00pm EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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Importance: High

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3. The number of unevaluable pts is higher than expected and could potentially impact the association between response rate and PD-L1 staining. Please state the number of patients in each group (N = 226, N = 161) who were un-evaluable due to: < 100 tumor cells in sample, tissue detachment from the slide, unacceptable control, decalcified tissue sample, and no sample received.

Please provide a timeline for your responses to our queries.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/22/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, March 21, 2017 3:16 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request
Importance: High

Dear Jennifer:

As we continue with our review of EMD's Original BLA for avelumab, the clinical reviewer has the following request for information:

- Patient (b) (6) has a death reason listed in ADSL as primary cause unknown; however, there is no death date and no death flag. Please clarify if this patient is alive or not, and please clarify reason for death.

Please provide a response to this query no later than **Thursday, March 23, 2017; 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/21/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, March 17, 2017 1:47 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--- Additional Clinical Information Request

Dear Jennifer:

Regarding EMD's Original BLA for avelumab, we have the following additional request for information:

CLINICAL INFORMATION REQUEST:

- Please provide additional details about the deaths of the following patients on-study, including narrative summaries:

(b) (6)

- Please provide narratives and CRFs for the following patients:

(b) (6)

- Pt (b) (6) has no AEs reported in ADAE, or in the tabulations AE dataset. Please confirm that the patients in fact had no adverse events on study. Please also provide a CRF for this patient.

Please provide responses to these queries by **Thursday, March 23, 2017, 3:00pm EST.**

Thank you,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
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U.S. Food and Drug Administration
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kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/17/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, March 17, 2017 1:34 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request

Hello Jennifer:

Relative to EMD's Original BLA for avelumab, please see the following clinical request for information:

CLINICAL INFORMATION REQUEST:

- Please provide an ADAE dataset with the June 9, 2016 data cutoff date where immune-related adverse events that were treated with systemic steroids are flagged.

Please provide this dataset by **March 23, 2017, 3:00pm EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
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kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/17/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, March 16, 2017 7:09 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--Clinical Information Request

Dear Jennifer:

Relative to EMD's Original BLA for avelumab, please see the following request for information from my clinical reviewers:

CLINICAL INFORMATION REQUEST:

- Please provide an ADAE dataset with the June 9, 2016 data cutoff date, where immune-related adverse events that were treated with systemic steroids are flagged.

Please provide this dataset by **March 24, 2017, 3:00pm EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/16/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, March 14, 2017 3:39 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Additional Clinical Information Request

Dear Jennifer:

Relative to EMD's Original BLA for avelumab, the clinical reviewer has the following additional request for information:

CLINICAL INFORMATION REQUEST:

We refer to our March 1, 2017 information request and to your March 6, 2017 reply. Please provide the following additional, detailed information:

In the 226 patients who have been followed for at least 13 weeks and in the 161 patients who have been followed for at least 24 weeks:

1. Please state the initial PD-L1 score and the results of rescoring for the 103/226 and 101/161 patients who were rescored.
2. Please state the number of patients who were retested in each group (N = 226, N = 161) and the reason for retesting (e.g., < 150 cells on H&E, unacceptable control, technical factors such as tissue detachment from the slide or tissue folding on the slide, section tested for PD-L1 inconsistent with H&E screening slide, < 100 cells on PD-L1 stained section, and clinical requests. Please provide the USUBJID for the patients who were retested due to clinical request.
3. The number of unevaluable pts is higher than expected and could potentially impact the association between response rate and PD-L1 staining. Please state the number of patients in each group (N = 226, N = 161) who were un-evaluable due to: < 100 tumor cells in sample, tissue detachment from the slide, unacceptable control, decalcified tissue sample, and no sample received.

Please provide a timeline for your responses to our queries.

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
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U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



APPEARS THIS WAY ON ORIGINAL

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/s/

KIM J ROBERTSON
03/14/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, March 14, 2017 3:11 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab----Additional Clinical Request

Dear Jennifer:

Relative to EMD's Original BLA for avelumab, the clinical reviewer has the following additional request for information:

CLINICAL INFORMATION REQUEST:

- Please submit certification that you have acted with due diligence, but were unable to obtain the missing financial disclosure information from the investigators as listed in section 1.3.4. of the BLA submission (option 3 on FORM FDA 3454).
- Please submit this certification and include a table listing the investigators for whom financial disclosure information is missing and the reason why it was not obtained. Please specify whether any of these investigators enrolled patients in either of the urothelial carcinoma cohorts.

Please provide responses to address these queries no later than **Friday, March 24, 2017, 3:00pm EST.**

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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/s/

KIM J ROBERTSON
03/14/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, March 14, 2017 2:54 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Excellent. Thank you Jennifer.
K

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Tuesday, March 14, 2017 2:29 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Hi Kim –

I acknowledge receipt of the request. We will respond by Friday. Regards, Jennifer

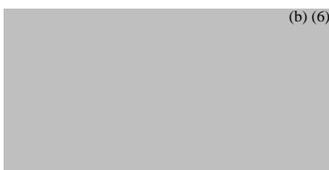
From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, March 14, 2017 2:20 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

Relative to EMD Serono's Original BLA 761078; avelumab, my clinical reviewer has the following request for information:

CLINICAL INFORMATION REQUEST:

Please confirm that these 9 patients, and no additional patients, received only neoadjuvant/adjvant therapy prior to study entry:



Please provide us with a response to this query by **Friday, March 17, 2017, 3:30pm EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

**Division of Oncology Products 1
Office of Oncology and Hematology Products
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Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/14/2017



BLA 761078

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Jennifer Stevens, JD
Global Regulatory Program Lead, Immuno-Oncology

Dear Ms. Stevens:

Please refer to your Biologics License Application (BLA) dated December 24, 2016, received December 27, 2016, submitted under section 351(a) of the Public Health Service Act for Avelumab, 20mg/ml.

We also refer to your correspondence dated and received January 17, 2017, 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 January 17, 2017, 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 Frances Fahnbulleh at (301) 796-0942. For any other information regarding this application, contact Kim Robertson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1441.

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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
03/10/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, March 08, 2017 2:09 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--Mid Cycle Communication Meeting Agenda
Attachments: Final 09March17 Mid Cycle Communication Meeting Agenda BLA 761078
avelumab.doc

Importance: High

Dear Jennifer:

Please see the attached Word .doc, as it contains the agenda for our March 9, 2017 Mid Cycle Communication Meeting with EMD Serono, Inc.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



PDUFA V Program Mid-Cycle Communication Agenda Template

Meeting Date: Thursday, March 9, 2017, 11:00am-12:00pm, EST
Application Number: BLA 761078
Product: Bavencio™ (avelumab)
Applicant Name: EMD Serono, Inc.
Proposed Indication: BAVENCIO is a programmed death ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy.

FDA Attendees:

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Supervisory Associate Director, DOP1
V. Ellen Maher, MD, Cross Discipline Team Leader, DOP1
Chana Weinstock, MD, Clinical Reviewer, DOP1
Nan Zheng, PhD, Clinical Pharmacology Reviewer, DPM/OCP
Pengfei Song, PhD, Clinical Pharmacology Team Leader, DCP5/OCP
Jingyu Yu, PhD, Pharmacometrics Team Leader, DPM/OCP
Joyce Cheng, PhD, Biometrics Reviewer, DBV
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Wei Chen, PhD, Non-Clinical Reviewer, DHOT
Todd Palmby, PhD, Non-Clinical Team Leader, DHOT
Kim J. Robertson, Regulatory Health Project Manager, DOP1

EMD Serono, Inc Attendees:

Kevin Chin, MD, Vice President, Immuno-Oncology, EMD Serono
Galit Rosen, MD, Medical Director, Immuno-Oncology, EMD Serono
Marcis Bajars, MD, Medical Director, Immuno-Oncology, Merck KGaA
Jacques Mascaro, PhD, Sr. VP, Head of Global Regulatory Affairs & R&D Quality
Jennifer Stevens, JD Global Regulatory Prog Lead, Immuno-Oncology, EMD Serono
Philippe Serrano, PhD, Head of Regulatory Immuno-Oncology/Oncology, EMD Serono
Junyuan Julia Xiong, MS, Assoc. Director, Global Biostatistics, EMD Serono
Byron Robinson, PhD, JD, Avelumab Program Lead, EMD Serono
Helga Koch, PhD, Director, Global Drug Safety, Merck KGaA
Joleen White, PhD, Assoc Director, Global Early Development, EMD Serono
Yulia Vugmeyster, PhD, Clinical Pharmacologist, EMD Serono
Stefanie Fischer, Principal Clinical Data Sciences, Merck KGaA
Dagmar Kottig-Roth, PhD, Senior Data Standards and Governance Mgr, Merck KGaA
Michael Bui, DDS, JD, MPH, Director, Global Regulatory Affairs
Christian Wrehlke, PhD, MDRA, Assoc. Director, Labeling
Shannon Dauksis, PharmD, PMP, R&D Project Manager
Laurie Strawn, PhD, Pfizer, Global Reg Portfolio Lead, Immuno-Onc./GU Malignancies

EMD Serono, Inc Attendees (cont.):

Andy Blake-Haskins, PharmD, Pfizer, Asset Team Lead

1. 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.

2. Significant Review Issues

We have identified the following significant review issues. These may be able to be addressed via the following post-marketing commitments (PMCs):

1. The proposed dose of avelumab (10 mg/kg IV every two weeks) may not be optimized for efficacy and there may be room to evaluate a higher dose. (b) (4)

Study EMR100070-005, a Phase 3 study in first line NSCLC

(b) (4)

- Consider submitting the complete efficacy and safety results of this novel dosing schema to the BLA as a post-marketing commitment.
 - If no substantial safety issues are identified in (b) (4) of Study 005, a clinical study should be considered to evaluate efficacy and safety in patients with UC at a higher AUC of avelumab.
2. To present data on the maximum number of patients, the primary efficacy analysis population that we plan to use for this indication will be patients dosed for 13 weeks or

more, with efficacy data based on the June 9, 2016 data cutoff date and datasets submitted to BLA #761078 on January 23, 2017, Serial No. 0004. This will result in different efficacy analyses than those presented in the current PI.

3. Information Requests

- There are no outstanding information requests.
- We will have additional information requests later in the week.

4. Major Safety Concerns

All major safety concerns can be addressed through review of the submission and the responses to our information requests.

5. Risk Management Update:

A REMS will not be required.

6. Advisory Committee Meeting Plans:

An Advisory Committee meeting is not planned.

7. Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones

This application has been identified for early action under an expedited review. We intend to send you the Late Cycle Meeting (LCM) background package by Wednesday, April 5, 2017. The Late Cycle Meeting is currently scheduled for Friday, April 7, 2017; 3:00pm- 4:00pm, Eastern Standard Time. You may choose to change this face-to-face meeting to a teleconference, or cancel the meeting altogether if you feel it is not needed given our continued and regular communications.

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/s/

KIM J ROBERTSON
03/08/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, March 07, 2017 12:43 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

Relative to EMD's BLA for avelumab, the clinical reviewer has the following request for information:

CLINICAL INFORMATION REQUEST:

The following stages are recorded at study entry. Some of these do not appear to be pts with locally advanced or metastatic disease.

Please verify that these stages are correct and that the pts do not have higher stage disease. Please also state the meaning of cM0(i+), M1a, and M1b in bladder cancer.

| | | | | |
|-----|--|---------|----|-----|
| 1. |  | MX | N0 | T1 |
| 2. | | M0 | N1 | T3 |
| 3. | | MX | N0 | T3b |
| 4. | | M0 | N1 | T3 |
| 5. | | cM0(i+) | N2 | T2a |
| 6. | | MX | N1 | T1 |
| 7. | | MX | N2 | T3 |
| 8. | | M0 | N1 | T2 |
| 9. | | M0 | N1 | T3 |
| 10. | | M0 | N1 | TX |
| 11. | | M0 | N1 | T3b |

Please provide us with a response to address these queries by Friday, March 24, 2017, 3:00pm EST.

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/07/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, March 06, 2017 4:54 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; Midcycle Communication Meeting Participants

Excellent. Thank you Jennifer.
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Monday, March 06, 2017 4:43 PM
To: Robertson, Kim
Subject: RE: BLA 761078; Midcycle Communication Meeting Participants

Hi Kim,
Yes, I can create a list with names/roles in the program. Let me try to get this for you tomorrow. Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, March 06, 2017 4:25 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; Midcycle Communication Meeting Participants

Dear Jennifer:

Would you be able to provide me with a list of EMD Serono attendees who intend on participating in the March 9, 2017 Mid-Cycle Communication Meeting?

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1

Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/06/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, March 06, 2017 1:42 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

Dear Jennifer:

Yes; thank you very much for the responses provided to our IRs to date relative to EMD's BLA. If we have any additional requests for information, I will be certain to let you know.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Monday, March 06, 2017 12:26 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

Thank you, Kim. We have now answered every outstanding information request (13 in all). I was just going back to check for your confirmations b/c I recall one where I did not receive an acknowledgement. If you believe you are missing any, please let me know. Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, March 06, 2017 12:10 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

OK; I believe we're on the same page now Jennifer. I think our e-mails might have been crossing. I presume you're referring to the e-mail that EMD is entitling "Response to FDA Request for Information No. 13_03_March 2017 .pdf", correct? If this is so, then yes; I am in receipt of that. I did open the .pdf and I saw what appeared to be screenshots.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
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Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Monday, March 06, 2017 11:59 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

Kim – That is one of the responses I sent this morning – complete with screen shots – that I was asking you to acknowledge. Thanks, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, March 06, 2017 11:57 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

Dear Jennifer:

To clarify,if EMD could indicate for us where the CRFs are in the application, with the June 9th cutoff, that would be most helpful.

Thank you,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Friday, March 03, 2017 4:37 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please
Importance: High

Dear Kim – We are unclear on FDA’s request below.

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Subject: RE: BLA 761078; avelumab---Clinical Information Request

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Regulatory Health Project Manager

Division of Oncology Products 1



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/s/

KIM J ROBERTSON
03/06/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, March 06, 2017 12:10 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

OK; I believe we're on the same page now Jennifer. I think our e-mails might have been crossing. I presume you're referring to the e-mail that EMD is entitling "Response to FDA Request for Information No. 13_03_March 2017 .pdf", correct? If this is so, then yes; I am in receipt of that. I did open the .pdf and I saw what appeared to be screenshots.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Monday, March 06, 2017 11:59 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

Kim – That is one of the responses I sent this morning – complete with screen shots – that I was asking you to acknowledge. Thanks, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, March 06, 2017 11:57 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

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03/06/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, March 06, 2017 12:04 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

Thank you for this information as well. I will forward this to the requesting reviewer also.

Regards,
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Dear Kim-

Please find attached a courtesy copy of our response to the Information Request below. This response will be submitted to the BLA on or before tomorrow, March 7, 2017.

Regards, Jennifer

From: Robertson, Kim [mailto:Kim.Robertson@fda.hhs.gov]
Sent: Monday, February 27, 2017 1:10 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab---Clinical Information Request
Importance: High

Dear Jennifer:

With regards to EMD Serono's BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

We have several concerns about your radiology charter:

1. Our understanding is that the radiologist will determine response after completing the tumor measurements. Please confirm if that is correct. Please identify the dataset containing only the radiologist's tumor measurements with the radiologist-determined response. If this has not been provided or is not readily available, please provide a date for its submission.
2. Our understanding is that the 2 oncologists will meet and determine response and that the 2 oncologists will then meet with the radiologist and also determine response. Please confirm that there are 2 determinations of response. Please state which datasets contain these response determinations.
3. For any pts in which the final response is different than the radiologist's response, please provide a table containing the radiologists response, final response, and the reason for the change.
4. Patients with lesions in areas that were not imaged at baseline were considered to have progressive disease. However, if these lesions were thought to be present at baseline, the patient was not considered to have progressive disease. Please state whether this occurred in the urothelial cancer cohort. If so, please provide the patient number, the date of the new lesion, and the reason this new lesion was not considered disease progression.
5. Please confirm that all patients, both from the initial 44 patients in the secondary expansion cohort as well as the 117 patients from the efficacy expansion cohort, indeed had their scans reviewed centrally.

Please provide responses to these queries by **Thursday, March 2, 2017, 3:00pm EST**. If for some reason you are unable to reply by **March 2, 2017**, please provide a proposed date for your reply.

Regards,
~Kim

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Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
03/06/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, March 06, 2017 11:36 AM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request -

I can certainly do that Jennifer..... allow me to look for them first and then I'll confirm receipt for each of the e-mails.

~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Monday, March 06, 2017 11:06 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request -
Importance: High

Kim- I left you a voicemail this morning – ignore this request but could you please confirm receipt of both of my submissions from this morning? Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, March 06, 2017 10:59 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please

Dear Jennifer:

I logged off a little earlier on Friday, which is why I didn't respond to you right away. Please allow me to defer to the requesting clinician for the clarification you seek and I will provide it to you as soon as I have it.

~Kim

Kim J. Robertson

Regulatory Health Project Manager



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Friday, March 03, 2017 4:37 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Need clarification please
Importance: High

Dear Kim – We are unclear on FDA’s request below.

Is FDA looking for ALL CRFs and only seeing March? If so, an easy fix because the June ones are in the BLA (and we can point FDA to the correct file containing them). Or, instead -

Is FDA looking for those CRFs in the IR to be corrected ? (I have cut and pasted the request below).

We are unclear. Thank you for your helping us to straighten this out!

Regards, Jennifer

CLINICAL REQUEST FOR INFORMATION:

We have multiple concerns about the derivation of the date of study drug discontinuation in the disposition dataset. For example:

- Patient [REDACTED] discontinued due to AE #2 on [REDACTED]. This corresponds to fatigue in the CRFs which began on [REDACTED]. The dates do not appear to be correct since the AE onset was after the discontinuation date. The pt also had a grade 2 infusion reaction with the 1st and only dose on [REDACTED].
- Patient [REDACTED] discontinued avelumab due to AE #10 on [REDACTED]. In the CRF, AE #10 corresponds to a grade 5 CVA. However, this occurred on [REDACTED]. A grade 1 CVA (?) is also reported in this pt from [REDACTED] with no change in dosing.
- Patient [REDACTED] discontinued avelumab due to AE #4 on [REDACTED]. In the CRF, AE #4 correspond to grade 5 sepsis. However, this occurred on [REDACTED]. There is also a report of sepsis at a lower grade on [REDACTED]. The only AE on [REDACTED] is constipation.

There are several pts whose AE onset date is after the date of discontinuation. In a few of these pts, the same AE was present at a lower grade at an earlier time point. However, this still does not correspond to the date of discontinuation.

- Patient [REDACTED] discontinued avelumab due to AE #11 on [REDACTED]. In the CRF, AE #11 correspond to fatigue on [REDACTED]. The CRF states that this resulted in drug interruption, but

the AE dataset says that this resulted in drug withdrawn. We are concerned that the AE dataset does not reflect the data in the CRF.

Please provide a plan to identify and address the issue with the date of discontinuation of study treatment. Please provide a plan to ensure that the dates in the CRFs correspond to the dates of these events in the datasets. Please provide a timeline to address these issues.

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, March 03, 2017 3:42 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Sure Jennifer; a zip file should be adequate. Let's try that avenue to see if that works.

Thank you,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Friday, March 03, 2017 3:06 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Hi Kim – I acknowledge your request and am checking on how quickly this can be done. When we have these ready to submit to the BLA, should I also send a zipped file to you to get these to the reviewer faster? It takes minimum 1 day to publish materials and send through the gateway. (We are talking about 242 CRFs here). Please advise. Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, March 03, 2017 2:29 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

As we continue with our review of EMD's BLA for avelumab, the clinical reviewer has ascertained need of the following:

CLINICAL INFORMATION REQUEST:

- Please provide updated CRFs that use the same data cutoff date as the datasets (i.e. June 9, 2016). These should be provided as soon as possible to avoid a major amendment.

Please provide a date as to when you are able to submit these materials.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

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/s/

KIM J ROBERTSON
03/06/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, March 03, 2017 2:29 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

As we continue with our review of EMD's BLA for avelumab, the clinical reviewer has ascertained need of the following:

CLINICAL INFORMATION REQUEST:

- Please provide updated CRFs that use the same data cutoff date as the datasets (i.e. June 9, 2016). These should be provided as soon as possible to avoid a major amendment.

Please provide a date as to when you are able to submit these materials.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

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kim.robertson@fda.hhs.gov



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KIM J ROBERTSON
03/03/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, March 02, 2017 3:57 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

My clinical team leader notified me that she was unable to find patient [REDACTED] (b) (6) in the tr.xpt and tu.xpt datasets, when she set EPOCH to screening. She realizes now that this patient had a baseline scan on Day 1 and the EPOCH was labeled as treatment. We apologize for any confusion this may have caused.

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Wednesday, March 01, 2017 12:18 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Dear Kim,

With regard the 2nd bullet point below regarding patient [REDACTED] (b) (6):

Both our programming group and DM are able to find this patient in the TR and TU datasets. This patient has 16 Records in TU and 37 records in TR.

Please see the screen shot below to assist the reviewer (I have attached a WORD doc which may be easier to read). If there is still a problem, please advise. Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, March 01, 2017 9:14 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab----Clinical Information Request

Dear Jennifer:

With regards to EMD Serono's BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

- Do you have any plans to develop a higher dose of avelumab in urothelial cancer? Do you have any plans you have to develop a higher dose of avelumab in other malignancies? If so, please provide your comments on those plans.
- Patient [REDACTED] (b) (6) is missing from the tr.xpt and tu.xpt datasets submitted January 23, 2017, but is included in the analysis datasets. Please state whether this patient should be included in the tabulation datasets and, if so, please provide revised datasets. If revised datasets are necessary, provide a timeline for the submission.

Please provide responses to address these queries by **Friday, March 3, 2017, 12Noon EST.**

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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KIM J ROBERTSON
03/02/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, March 01, 2017 1:56 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab--- Filing Status-MCM Info

Dear Jennifer:

Yes; our Mid-Cycle Communication Meeting (MCM) to discuss any issues/concerns we may have with EMD Serono's avelumab BLA up to that point, has been scheduled for **Thursday, March 9, 2017, 11:00am -12:00Noon, EST**, barring no unexpected issues arise during the review of the BLA. Please use the following call-in information:

Dial: Local: 1-301-796-7777
Toll free: 1-855-828-1770

Meeting ID: (b) (4)

This meeting is primarily intended to provide EMD with a sense of any substantive review issues/concerns identified with the avelumab BLA up to the mid-point in the review process, and to assist EMD to efficiently respond to any information requests that *may be* outstanding at that point, to discuss any Major Safety Concerns and Risk Management Updates, and to briefly touch on the Late Cycle Meeting (if one is so desired by EMD). Approximately 2 days prior to the MCM, I intend on sending you a more concise, detailed agenda.

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Wednesday, March 01, 2017 11:34 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab--- Filing Status

Dear Kim,

In the filing letter, FDA stated its intended date for the internal mid-cycle meeting is Monday, March 6, 2017. Do you yet have a proposed date for the communication call with the Sponsor regarding put from this this meeting? Thank you,
Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, February 27, 2017 5:58 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab--- Filing Status
Importance: High

Dear Jennifer:

Please see the attached .pdf document, as it is a courtesy copy of the Filing Status of EMD Serono's Original BLA #761078 for avelumab.

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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KIM J ROBERTSON
03/02/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, March 01, 2017 10:58 AM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

The reviewer's clarification is as follows:

The 117 patients mentioned in the original Information Request refer to the patients in the efficacy expansion cohort who were platinum non-naïve and who had 6 months or greater of follow-up.

Please also clarify if all 182 patients in the efficacy expansion cohort, who were platinum non-naïve and who had 13 weeks or greater of follow-up, had their scans reviewed centrally.

Thank you,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Wednesday, March 01, 2017 10:17 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request

Dear Kim-

To respond to this request, we are waiting for data from our CRO and are not likely to be able to meet the Friday requested deadline. Our goal is to submit the response on Monday if at all possible but no later than Tuesday, March 7, 2017.

With regard to the 117 patients referenced in question 5 below: we believe this could be a typographical error as we have no dataset with that number. The number of the subjects in the efficacy population is 242 (after subtracting the cisplatin naïve as requested by FDA) with 198 in the efficacy expansion cohort.

Could you please confirm that we have understood FDA's intent in question number 5?

Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Monday, February 27, 2017 1:10 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab---Clinical Information Request
Importance: High

Dear Jennifer:

With regards to EMD Serono's BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

We have several concerns about your radiology charter:

1. Our understanding is that the radiologist will determine response after completing the tumor measurements. Please confirm if that is correct. Please identify the dataset containing only the radiologist's tumor measurements with the radiologist-determined response. If this has not been provided or is not readily available, please provide a date for its submission.
2. Our understanding is that the 2 oncologists will meet and determine response and that the 2 oncologists will then meet with the radiologist and also determine response. Please confirm that there are 2 determinations of response. Please state which datasets contain these response determinations.
3. For any pts in which the final response is different than the radiologist's response, please provide a table containing the radiologists response, final response, and the reason for the change.
4. Patients with lesions in areas that were not imaged at baseline were considered to have progressive disease. However, if these lesions were thought to be present at baseline, the patient was not considered to have progressive disease. Please state whether this occurred in the urothelial cancer cohort. If so, please provide the patient number, the date of the new lesion, and the reason this new lesion was not considered disease progression.
5. Please confirm that all patients, both from the initial 44 patients in the secondary expansion cohort as well as the 117 patients from the efficacy expansion cohort, indeed had their scans reviewed centrally.

Please provide responses to these queries by **Thursday, March 2, 2017, 3:00pm EST**. If for some reason you are unable to reply by **March 2, 2017**, please provide a proposed date for your reply.

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

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KIM J ROBERTSON
03/01/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, March 01, 2017 9:06 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--- Clinical Information Request
Importance: High

Dear Jennifer:

With regards to EMD Serono's BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

We have multiple concerns about the derivation of the date of study drug discontinuation in the disposition dataset. For example:

- Patient (b) (6) discontinued due to AE #2 on (b) (6). This corresponds to fatigue in the CRFs which began on (b) (6). The dates do not appear to be correct since the AE onset was after the discontinuation date. The pt also had a grade 2 infusion reaction with the 1st and only dose on (b) (6).
- Patient (b) (6) discontinued avelumab due to AE #10 on (b) (6). In the CRF, AE #10 corresponds to a grade 5 CVA. However, this occurred on (b) (6). A grade 1 CVA (?) is also reported in this pt from (b) (6) with no change in dosing.
- Patient (b) (6) discontinued avelumab due to AE #4 on (b) (6). In the CRF, AE #4 correspond to grade 5 sepsis. However, this occurred on (b) (6). There is also a report of sepsis at a lower grade on (b) (6). The only AE on (b) (6) is constipation.

There are several pts whose AE onset date is after the date of discontinuation. In a few of these pts, the same AE was present at a lower grade at an earlier time point. However, this still does not correspond to the date of discontinuation.

- Patient (b) (6) discontinued avelumab due to AE #11 on (b) (6). In the CRF, AE #11 correspond to fatigue on (b) (6). The CRF states that this resulted in drug interruption, but the AE dataset says that this resulted in drug withdrawn. We are concerned that the AE dataset does not reflect the data in the CRF.

Please provide a plan to identify and address the issue with the date of discontinuation of study treatment. Please provide a plan to ensure that the dates in the CRFs correspond to the dates of these events in the datasets. Please provide a timeline to address these issues.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

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KIM J ROBERTSON
03/01/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, February 27, 2017 5:58 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--- Filing Status
Attachments: Final No Filing Review Issues Identified BLA 761078 (COR-NDAFILE-05)(COR-SNDAFILE-05)(COR-BLAFILE-05)(COR-SBLAFILE-05).pdf

Importance: High

Dear Jennifer:

Please see the attached .pdf document, as it is a courtesy copy of the Filing Status of EMD Serono's Original BLA #761078 for avelumab.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

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KIM J ROBERTSON
02/27/2017

Robertson, Kim

From: Robertson, Kim
Sent: Monday, February 27, 2017 1:10 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request
Importance: High

Dear Jennifer:

With regards to EMD Serono's BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

We have several concerns about your radiology charter:

1. Our understanding is that the radiologist will determine response after completing the tumor measurements. Please confirm if that is correct. Please identify the dataset containing only the radiologist's tumor measurements with the radiologist-determined response. If this has not been provided or is not readily available, please provide a date for its submission.
2. Our understanding is that the 2 oncologists will meet and determine response and that the 2 oncologists will then meet with the radiologist and also determine response. Please confirm that there are 2 determinations of response. Please state which datasets contain these response determinations.
3. For any pts in which the final response is different than the radiologist's response, please provide a table containing the radiologists response, final response, and the reason for the change.
4. Patients with lesions in areas that were not imaged at baseline were considered to have progressive disease. However, if these lesions were thought to be present at baseline, the patient was not considered to have progressive disease. Please state whether this occurred in the urothelial cancer cohort. If so, please provide the patient number, the date of the new lesion, and the reason this new lesion was not considered disease progression.
5. Please confirm that all patients, both from the initial 44 patients in the secondary expansion cohort as well as the 117 patients from the efficacy expansion cohort, indeed had their scans reviewed centrally.

Please provide responses to these queries by **Thursday, March 2, 2017, 3:00pm EST**. If for some reason you are unable to reply by **March 2, 2017**, please provide a proposed date for your reply.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

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/s/

KIM J ROBERTSON
02/27/2017

Robertson, Kim

From: Robertson, Kim
Sent: Friday, February 24, 2017 9:31 AM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Request prompt response

Dear Jennifer:

The clinician informed me that the conversion exercise that you have proposed to address Question 1(b) for the calculation of MSKCC score is acceptable.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

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Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Friday, February 24, 2017 8:47 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Request prompt response

Thank you, Kim!

From: Robertson, Kim [mailto:Kim.Robertson@fda.hhs.gov]
Sent: Friday, February 24, 2017 8:42 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Request prompt response

Dear Jennifer:

Please allow me to get the clarification you seek. As soon as I do, I will provide it to you.

Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Friday, February 24, 2017 7:10 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Clinical Information Request - Request prompt response

Dear Kim,

We have a follow-up question to FDA's request below.

Regarding generating a dataset containing a baseline prognostic score based on the MSKCC scoring algorithm: EMD Serono cannot provide this as only ECOG scores were collected in this study; Karnofsky scores were not collected.

We are aware that sometimes a conversion rule is applied to map ECOG to Karnofsky scores (<http://oncologypro.esmo.org/Guidelines-Practice/Practice-Tools/Performance-Scales>). Please advise as to whether FDA would like us to undertake this conversion exercise to provide a response to question 1(b) below.

We would appreciate a response as soon as possible today.

Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Thursday, February 23, 2017 2:57 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

With regard to EMD Serono's newly submitted BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

1. Please submit a dataset in which you provide a calculated baseline prognostic score for all 161 patients included in the ≥ 6 months follow-up group according to both Bellmunt and MSKCC prognostic scores. For identifying sites of disease, please use IRC-identified sites of disease (and not investigator-assessed sites).
 - a. The Bellmunt system - PS > 0 , Hgb < 10 g/dL, and liver mets (Y/N). This score is 0-3.
 - b. The MSKCC system - PS $< 80\%$ and visceral disease (Y/N). Visceral disease is defined as lung, liver, or bone. The score is 0-2.
2. Please comment on the efforts and investigations that you have undertaken to identify the difference in Confirmed ORR in PD-L1 positive vs. PD-L1 negative patients, especially in the 1%

and 5% tumor cells with $\geq 1+$ groups) between the initial 44 patients (secondary expansion cohort) and the subsequent patients (efficacy expansion cohort). Please comment whether these efforts have attempted to identify possible differences such as a change in the entry criteria, biopsy requirements (fresh vs. frozen, pre-vs. post therapy, primary vs. metastatic sites), samples that were submitted for the assay, change in the test, change in who is scoring the test, etc.?

Please provide responses to these inquiries by **Wednesday, March 1, 2017, 3:00pm EST.**

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

**Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration**
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
02/24/2017



BLA 761078

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

EMD Serono, Inc.
Attention: Jennifer Stevens, JD
Global Regulatory Program Lead, Immuno-Oncology
One Technology Place
Rockland, MA 02370

Dear Ms. Stevens:

Please refer to your Biologics License Application (BLA) dated December 23, 2016, received December 27, 2016, submitted under section 351(a) of the Public Health Service Act for Bavencio™ (avelumab), Intravenous, 20 mg/mL, 10 mg/kg.

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 August 27, 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>.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

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 April 5, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and post-marketing requirement/commitment requests. In addition, the planned date for our internal mid-cycle review meeting is March 6, 2017. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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 [PLLR Requirements for Prescribing Information](#) websites including:

- 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.

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

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), Medication Guide, and patient PI (as applicable). 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), Medication Guide, and patient PI (as applicable), 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.

We reference the waiver granted to Pfizer for IND [REDACTED] ^{(b) (4)} for the pediatric study requirement for this application.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GEOFFREY S KIM
02/24/2017



BLA 761078

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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

ATTENTION: Jennifer Stevens, JD
Global Regulatory Program Lead, Immuno-Oncology

Dear Ms. Stevens:

Please refer to your Biologics License Application (BLA) dated December 24, 2016, received December 27, 2016, submitted under section 351(a) of the Public Health Service Act for Avelumab, 20mg/ml.

We acknowledge receipt of your correspondence dated and received January 17, 2017, requesting a review of your proposed proprietary name, Bavencio.

If the application is filed, the user fee goal date will be April 17, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, please contact me at (301) 796-0942. For any other information regarding this application, contact Kim Robertson, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Frances Fahnbulleh, PharmD, RPh.
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

FRANCES G FAHNBULLEH
02/23/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, February 23, 2017 2:57 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

With regard to EMD Serono's newly submitted BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

1. Please submit a dataset in which you provide a calculated baseline prognostic score for all 161 patients included in the ≥ 6 months follow-up group according to both Bellmunt and MSKCC prognostic scores. For identifying sites of disease, please use IRC-identified sites of disease (and not investigator-assessed sites).
 - a. The Bellmunt system - PS > 0, Hgb < 10 g/dL, and liver mets (Y/N). This score is 0-3.
 - b. The MSKCC system - PS < 80% and visceral disease (Y/N). Visceral disease is defined as lung, liver, or bone. The score is 0-2.
2. Please comment on the efforts and investigations that you have undertaken to identify the difference in Confirmed ORR in PD-L1 positive vs. PD-L1 negative patients, especially in the 1% and 5% tumor cells with $\geq 1+$ groups) between the initial 44 patients (secondary expansion cohort) and the subsequent patients (efficacy expansion cohort). Please comment whether these efforts have attempted to identify possible differences such as a change in the entry criteria, biopsy requirements (fresh vs. frozen, pre-vs. post therapy, primary vs. metastatic sites), samples that were submitted for the assay, change in the test, change in who is scoring the test, etc.?

Please provide responses to these inquiries by **Wednesday, March 1, 2017, 3:00pm EST.**

Regards,
~Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
02/23/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, February 22, 2017 1:55 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---Clinical Information Request

Dear Jennifer:

With regards to EMD Serono's BLA for avelumab, please see the following request for information from the reviewing clinician:

CLINICAL REQUEST FOR INFORMATION:

- For 67 patients screened but not treated on the UC cohorts, the reason for screen failure is listed in the dataset ADSL as "did not meet eligibility criteria". Please comment on the availability of additional data on specific eligibility criteria not met in each case. Please provide these data where known.

Please provide a response to address this query by **Monday, February 27, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
02/22/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, February 21, 2017 3:49 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab--Clinical Information Request

Dear Jennifer:

In EMD Serono's submission to BLA #761078 dated January 20, 2017; received January 23, 2017, under section 5.3.5.1 there is a dataset entitled Adverse Events AD.

1. In this dataset there is a column entitled TRTEMFL, which is the treatment emergent analysis flag. In 302 rows, there is no flag (i.e. the cell is blank rather than stating "Y"). Please clarify if these were actually treatment emergent adverse events? For example, patient (b) (6) had an immune-mediated thyroiditis that is not flagged as treatment emergent. Please explain this discrepancy.
2. Please clarify if any of these adverse events occurred prior to treatment.
3. Please also clarify why there is a negative value for ASTDY in 164 rows.

Please provide a response to address this request for information by **Thursday, February 23, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
02/21/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, January 25, 2017 4:30 PM
To: 'Jennifer Stevens'
Subject: RE: BLA #761078; avelumab---Clinical Information Request - RESPONSE REQUESTED

Hello Jennifer:

Please note that for Question #2, we are in fact seeking information for DMC minutes as opposed to IERC minutes.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Wednesday, January 25, 2017 3:03 PM
To: Robertson, Kim
Subject: RE: BLA #761078; avelumab---Clinical Information Request - RESPONSE REQUESTED
Importance: High

Dear Kim –

I acknowledge receipt of your request below. I would appreciate a clarification, however. Questions 1 and 3 deal with IERC. Question 2 asks about DMC minutes. **Could you please confirm that FDA is looking for DMC minutes as opposed to IERC minutes?**

I would appreciate your response as quickly as possible. Thank you, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Wednesday, January 25, 2017 1:21 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA #761078; avelumab---Clinical Information Request
Importance: High

Dear Jennifer:

Please provide us with the following information, as it pertains to EMD's BLA for avelumab:

CLINICAL INFORMATION REQUEST:

1. Provide a copy of the IERC Charter and any additional supporting documents related to the IERC function. If these have already been provided in the application, please indicate where they can be found.
2. Provide a copy of the DMC minutes and any additional related supporting documents. If these have already been provided in the application, please indicate where they can be found.
3. Please indicate which CRO performed the IERC.

Please provide us with this information no later than **Thursday, January 26, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
01/25/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, January 25, 2017 1:11 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors

Here is the information you need for your Pfizer colleague Jennifer:

Dial: Local: 1-301-796-7777
toll free: 1-855-828-1770

Follow the instructions that you hear on the phone.
Cisco Unified MeetingPlace **Meeting ID** [REDACTED] (b) (4)

~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Wednesday, January 25, 2017 11:50 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors

Hi Ki – Sorry for the delay. We would appreciate a call-in line for our Pfizer colleague.

From: Robertson, Kim [mailto:Kim.Robertson@fda.hhs.gov]
Sent: Wednesday, January 25, 2017 11:35 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: FW: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors
Importance: High

Good morning Jennifer:

Did you still need more time to verify the names of the AOM attendees and whether or not you'd like me to create a WebEx Number for any of your colleagues that *may* want to listen in on the Technical Walkthrough Meeting? If your meeting attendee list won't change, I can process our Lobbyguard system for you and your colleagues and have your barcode sent to you that you will need to bring to expedite your badging process.

Thank you,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Robertson, Kim
Sent: Tuesday, January 24, 2017 5:09 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors

Dear Jennifer:

To answer your first question regarding the second Technical Walkthrough meeting; no, that meeting will NOT take place during the OHOP Clinical Rounds. The OHOP Rounds will have concluded, before EMD presents, which is why they are keeping the topics of discussions for Rounds to a minimum to allow EMD Serono time to present. Upon the conclusion of the AOM, I will escort the 6 presenters back to the holding conference room to re-join the others, so we can get started right away with the Technical Walkthrough meeting. **ALL** of your colleagues can be in attendance of the Technical Walkthrough meeting, because it's a very specific meeting aimed at the core review team of the BLA only. Dr. Pazdur and many others will not need to be as aware of any details/intricacies involving the application like the core team and therefore, they will not participate at all. I can provide you with a call-in number for the Technical Walkthrough meeting, given the nature of that meeting. If you anticipate that anyone would like to call into that meeting, please let me know, so that I may generate a WebEx Number for you.

To address your second question; yes, you may provide me with your presentation slide-deck on Thursday. A few hardcopy printouts are fine if you choose to bring some, but I definitely need an electronic version for uploading for our staff that handles that for our presenters. If you can provide me with slides by Thursday afternoon, that would be most appreciative.

Please verify that your list of attendees of people, who wish to attend the meetings in person, has not changed.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research

U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Tuesday, January 24, 2017 1:58 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors

Hi Kim –

Thank you for the call and the information. I have a couple of questions that are coming out of this news.

First, you have confirmed that we will have a data/biostats discussion following the AOM. Will this also take place during Clinical rounds? In my recent experience with DOP2, the data/biostats meeting that followed did not involve exactly the same people at FDA (some FDAers from the AOM meeting left and another individual joined us). Can you please confirm this information because I may need to leave someone in the conference room that we need for that meeting, but not the presentation meeting.

Additionally, we will have to combine some presenters' information to cut down to 6 people. This means reworking slides. Because of this need, would it be possible to provide the slides to you on Thursday instead of Wednesday? We are happy to bring a large stack of printed copies as well as sending to you electronically if this would be helpful.

Thanks very much for your response, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, January 24, 2017 11:42 AM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors
Importance: High

Dear Jennifer:

It has just been brought to my attention that for AOMs, our Office Director is now asking that **ONLY 6** people be allowed entrance into our main Conference Room for the presentation/ Q&A. This is due in part because of space availability and to assist in the streamlining of the presentations. Therefore, any additional personnel that attends the AOM will have to wait in one of our reserved conference rooms. I wanted to let you know of this, prior to the meeting, in case it may have any impact on the number of people that need to attend the AOM. We recommend only those that will be key presenters attend the meeting. If you believe your list of attendees may change, please let me know, so that I may enter their names in our Lobbyguard database accordingly.

To reiterate, EMD Serono will be presenting at 1:30pm. Given that we anticipate EMD will be with us for quite a bit of the afternoon, if you would like to arrive a little earlier, perhaps around 11:30am, you and your colleagues can be escorted to our cafeteria to purchase lunch before the 1:30pm presentation. Do you believe this is something EMD would opt to do? If so, I will secure additional escort assistance for me on this day.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]

Sent: Thursday, January 19, 2017 2:10 PM

To: Robertson, Kim

Subject: RE: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors

Hi Kim – Here are the participants for the AOM meeting and the foreign visitor forms for the following participants:

Philippe Serrano

Junyuan Xiong

Achta Paraiso LeBourhis*

Helga Koch

Dagmar Kottig-Roth

*Final determination of Achta's attendance (CMC) depends upon your reply to my email of yesterday asking whether FDA will be bringing CMC people to this meet.

Also, is it acceptable to have 2 people call into this meeting? I can provide a phone webex if needed.

Thank you, Jennifer

List of Participants: 761078 AOM Meeting – Jan 27, 2017

| Name | Function/Company |
|----------------------------------|--|
| Kevin Chin, MD | Vice President, Immuno-Oncology, EMD Serono, Inc. |
| Yulia Vugmeyster, PhD | Clinical Pharmacologist, Clinical Pharmacology, EMD Serono, Inc. |
| Galit Rosen, MD | Medical Director, EMD Serono, Inc. |
| Berend Neuteboom, PhD | Senior Global Early Development Lead anti-PDL1 |
| Helga Koch, PhD | Director, Global Drug Safety, Merck KGaA |
| Achta Paraiso Le Bourhis, PharmD | Manager, Biotech Regulatory CMC Unit, Merck - Ares Trading S.A. |
| Philippe Serrano, PhD | Head of Global Regulatory Oncology, EMD Serono, Inc. |
| Dagmar Kottig-Roth, PhD | Senior Data Standards and Governance Manager, Merck KGaA |
| Jennifer Stevens, JD | Global Regulatory Program Lead, Immuno-Oncology, EMD Serono, Inc. |
| Junyuan (Julia) Xiong, MS | Associate Director, Global Biostatistics, EMD Serono, Inc.. |
| Michael Bui, DDS, JD, MPH | Director, Global Regulatory Affairs, EMD Serono, Inc. |
| Laurie Strawn, PhD | Global Regulatory Portfolio Lead Immuno-Oncology, Pfizer (via phone) |
| Andy Blake-Haskins, PharmD | Asset Team Lead, Pfizer (via phone) |



Confidential

2

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, January 17, 2017 2:52 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: FW: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors
Importance: High

Hello again Jennifer:

To add to my previous e-mail.....I will also need the names of ALL of the EMD Serono attendees expected to attend the AOM on January 27, 2017. I will need to enter their names into a separate database system that will assist in generating name badges for everyone. Please ensure that all parties bring a form of a photo ID (i.e., Driver's License, Passport, Green Card). If you have a list of those names already prepared, I will take them now. Otherwise, please provide them when you give me any Foreign Visitor's Forms you may have by January 19th.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Robertson, Kim

Sent: Tuesday, January 17, 2017 12:25 PM

To: Jennifer Stevens <jennifer.stevens@emdserono.com> (jennifer.stevens@emdserono.com)

Subject: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors

Importance: High

Dear Jennifer:

I'm not certain if Christy provided you a Foreign Visitor's Form for any of your EMD Serono colleagues, that may not be US Citizens, but if one was not provided to you, please see the attached Word .doc. **Please fill this out for any non-US Citizens and send it back to me no later than Thursday, January 19, 2017, 2:00pm EST.** It is imperative that we have these forms back on time, so they can be processed by our security personnel. Any non-US Citizens will not be allowed beyond our lobby area without prior proper screening, so I strongly recommend the form(s), if any, be sent back by the requested date.

On the day of your meeting, please arrive approx. **30mins.** early to avoid any unnecessary issues with parking and/or security screening. Please also provide me with your AOM presentation slides by **Wednesday, January 25, 2017, 3:30pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
01/25/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, January 25, 2017 1:21 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: BLA #761078; avelumab---Clinical Information Request
Importance: High

Dear Jennifer:

Please provide us with the following information, as it pertains to EMD's BLA for avelumab:

CLINICAL INFORMATION REQUEST:

1. Provide a copy of the IERC Charter and any additional supporting documents related to the IERC function. If these have already been provided in the application, please indicate where they can be found.
2. Provide a copy of the DMC minutes and any additional related supporting documents. If these have already been provided in the application, please indicate where they can be found.
3. Please indicate which CRO performed the IERC.

Please provide us with this information no later than **Thursday, January 26, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
01/25/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, January 25, 2017 9:39 AM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Information Request

Dear Jennifer:

Thank you for your confirmation.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Wednesday, January 25, 2017 9:05 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Information Request

Dear Kim –

I can confirm that the information below is correct – both location and contact. Regards, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, January 24, 2017 4:44 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab---Information Request
Importance: High

Dear Jennifer:

In the event that a sponsor inspection is warranted, we will need to know the sponsor's location for planning purposes. It should be the location of the Trial Master File for the study to be inspected: EMR 100070-001. Would you confirm if the information below that I saw on EMD's FDA Form 356h is what I'm in need of:

EMD Serono, Inc.
One Technology Place

Rockland, MA 02370
POC: Rosann Reinhart; rosann.reinhart@emdseron.com
Tel: (781) 681-2233

If this is not correct, please provide me with that information right away.

Thank you,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
01/25/2017

Robertson, Kim

From: Robertson, Kim
Sent: Tuesday, January 17, 2017 2:52 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: FW: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors
Attachments: FVDR Form for EMD Serono Inc AOM Tech Walkthrough.doc.docx
Importance: High

Hello again Jennifer:

To add to my previous e-mail.....I will also need the names of ALL of the EMD Serono attendees expected to attend the AOM on January 27, 2017. I will need to enter their names into a separate database system that will assist in generating name badges for everyone. Please ensure that all parties bring a form of a photo ID (i.e., Driver's License, Passport, Green Card). If you have a list of those names already prepared, I will take them now. Otherwise, please provide them when you give me any Foreign Visitor's Forms you may have by January 19th.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Robertson, Kim
Sent: Tuesday, January 17, 2017 12:25 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com> (jennifer.stevens@emdserono.com)
Subject: BLA 761078; avelumab---List of AOM Attendees/Potential Foreign Visitors
Importance: High

Dear Jennifer:

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without prior proper screening, so I strongly recommend the form(s), if any, be sent back by the requested date.

On the day of your meeting, please arrive approx. **30mins.** early to avoid any unnecessary issues with parking and/or security screening. Please also provide me with your AOM presentation slides by **Wednesday, January 25, 2017, 3:30pm EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
01/17/2017

Fahnbulleh, Frances

From: Fahnbulleh, Frances
Sent: Thursday, January 12, 2017 5:49 PM
To: 'jennifer.stevens@emdserono.com'
Cc: Robertson, Kim
Subject: BLA 761078 Avelumab

Dear Dr. Stevens,

Please refer to your recent submission for BLA-761078/SDN1, dated 12/27/2016. Although a proprietary name request for review (PNR) was included in your submission, the document room failed to code for PNR review due to incomplete information.

Please resubmit your proprietary name to the application following the procedure below to ensure that the document room codes for "Proprietary Name/Request for Review" accurately and opens an OSE PDUFA clock for the name review.

When submitting a proprietary name request for review to the Agency, it is crucial to:

- Check "Other" in Box 21 of the 356h form and write in "Proprietary Name/Request for Review"
- Additionally, include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters, at the top of your cover letter and on the top of the first page of the main submission document (refer to the complete submission guidance link below).
- Please clearly state in the cover letter and supporting documentation the exact name(s) you are requesting for review.

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>)

Respectfully,

Frances Fahnbulleh, RPh, PharmD

Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
CDER/FDA/W022, Rm#4404
Ph: 301-796-0942/Fax: 301-796-9832
Email: Frances.Fahnbulleh@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL

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/s/

FRANCES G FAHNBULLEH
01/12/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, January 12, 2017 2:26 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
(jennifer.stevens@emdserono.com)
Subject: New BLA 761078; Bavencio (avelumab)---Clinical Information Request
Importance: High

Dear Jennifer:

As our review of EMD Serono's BLA for UC remains underway, the clinical reviewer has ascertained the following request for information:

CLINICAL INFORMATION REQUEST:

- Please provide a dataset in the form of ADSL/baseline data on all 164 patients with >6 months of follow-up for whom data will be provided at the time of the planned efficacy update. Please flag those 152 patients who form the >6 month efficacy analysis population at the time of initial submission of the supplemental BLA.
- Please also comment on the anticipated date of the efficacy update that is to contain data on all 249 pts with urothelial cancer, which was to be submitted within 30 days of initial sBLA submission.

Please provide responses to address these clinical queries by **Wednesday, January 18, 2017.**

Please also confirm that you are in receipt of this inquiry and the inquiry sent to you on Wednesday, January 11, 2017.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



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KIM J ROBERTSON
01/12/2017

Robertson, Kim

From: Robertson, Kim
Sent: Wednesday, January 11, 2017 6:40 PM
To: 'Jennifer Stevens'
Subject: New BLA 761078; Bavencio (avelumab)--- Pharmacometrics Information Request
Importance: High

Dear Jennifer:

I am Kim Robertson; the Project Manager that my Chief Christy Cottrell informed you of. I will be managing the avelumab application for EMD Serono. I will be providing you/EMD with correspondence relative to this BLA relatively soon; however, as our initial evaluation of this application remains underway, please see the following request for information from our clinical pharmacology/pharmacometrics reviewer:

PHARMACOMETRICS REQUEST FOR INFORMATION:

Reference is made to "EMR 10070-001-002-003 Population PK report" (Module 5.3.3.5 in Sequence 0000, submitted on December 27, 2016). Please evaluate the potential time-varying clearance of avelumab given similar findings in previously approved PD1/PDL1 targeting treatments [see section 12.3 in the labels of TECENTRIQ (atezoliumab)

BLA 761041, OPDIVO (nivolumab) BLA 125544, and KEYTRUDA (pembrolizumab) BLA 125514]. The following model structure can be used to describe the time-dependent PK. Please submit the analysis results along with model codes and datasets for our review.

Time-varying PK model structure:

$$CL_{TPK} = TVCL \cdot e^{\frac{(C_{max} - C_{min}) \cdot Time}{T_{50} - T_{min}}} \cdot Cov \cdot e^{\epsilon}$$

Please provide a response to address this query by **Thursday, February 3, 2017, 3:00pm EST.**

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
01/11/2017

Cottrell, Christy L.

From: Cottrell, Christy L.
Sent: Wednesday, January 04, 2017 2:54 PM
To: 'jennifer.stevens@emdserono.com'
Cc: Robertson, Kim
Subject: BLA 761078 for avelumab: Information Request

Importance: High

Ms. Stevens,

The purpose of this email to introduce myself and convey an information request for your new BLA 761078 for avelumab. The Regulatory Project Manager assigned to manage this application is Kim Robertson. As she is currently out of the office, I am sending this message on her behalf. She is expected to return next week.

You submitted a clinsite.xpt file for this application (submitted 12/24) for load to CDER's Clinical Investigator Site Selection Tool (CISST), but on QC of loaded tool it is failing on multiple parameters. You have not provided sufficient detail in the associated "define" file to figure out exactly why clinsite.xpt data does not appear consistent with the clinical study reports and/or SDTM-ADAM datasets also submitted.

For example (not an all-inclusive list of QC fails):

1. Numbers of deaths reported in clinsite.xpt for each study are different from numbers reported in CSRs
2. For study EMR 100070-001 clinsite.xpt the UC arm contains 242 subjects (as does the "RESPONSE.xpt dataset in submission), but CSR state 241 subjects (safety population). The clinsite define file does not state population reported for enrolled or provide explanation of how derived.
3. For the study EMR 100070-001 non-UC arm, we are unable to determine how enrolled subjects reported in the clinsite.xpt file were defined or derived, and there does not appear to be any matching population reported in CSRs.

To resolve issues we request a more robust clinsite.xpt define file and/or BIMO reviewers guide that includes at minimum:

- Confirmation that data cut-off dates for CSRs and clinsite.xpt data are the same
- Additional explanation on how numbers of subjects enrolled in each arm, in each study were derived
- Additional explanation on how ORR, death, and discontinuation values were derived

We request a response as soon as possible. Please let us know your anticipated timeframe for responding.

Feel free to contact me with any questions.

Regards,
Christy Cottrell

Christy Cottrell

Chief, Project Management Staff

Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 301-796-4256

Fax: 301-796-9845
christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
01/04/2017



IND 115747

MEETING MINUTES

EMD Serono
Attention: Jennifer Stevens, JD
Global Program Lead, Regulatory, Immuno-Oncology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Stevens:

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 October 6, 2016. The purpose of the meeting was to discuss the planned BLA submission for avelumab for the proposed indication of advanced or metastatic urothelial cancer.

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 Charlene Wheeler, MSHS, Senior Regulatory Project Manager at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

{See appended electronic signature page}

Charlene Wheeler, MSHS
Senior Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
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

Meeting Date and Time: October 6, 2016, 3-4PM
Meeting Location: White Oak Building 22 Room 1315

Application Number: IND 115747
Product Name: avelumab
Indication: Urothelial cancer (UC)
Sponsor/Applicant Name: EMD Serono

Meeting Chair: V. Ellen Maher, MD
Meeting Recorder: Charlene Wheeler, MSHS

FDA ATTENDEES

| | |
|------------------------|-----------------------------------|
| Geoffrey Kim, MD | Director, DOP1 |
| Amna Ibrahim, MD | Deputy Director, DOP1 |
| V. Ellen Maher, MD | Clinical Team Leader, DOP1 |
| Chana Weinstock, MD | Medical Officer, DOP1 |
| Shenghui Tang, PhD | Biostatistics Team Leader |
| Laura Fernandes, PhD | Biostatistics Reviewer |
| Wimolnut Manheng, PhD | Pharm/Tox Reviewer, DHOT |
| Todd Palmby, PhD | Pharm/Tox Supervisor, DHOT |
| Aaron Schetter, MD | Medical Officer, CDRH |
| Charlene Wheeler, MSHS | Senior Regulatory Project Manager |

SPONSOR ATTENDEES

| | |
|----------------------------|--|
| Jacques Mascaro, PhD | Senior VP, Global Regulator Affairs and R&D Quality |
| Alise Reicin Boiarsky, MD | Head of Global Clinical Development |
| Reinhard Von Roemeling, MD | Senior VP, Global TA Head Oncology, Clinical Development |
| Byron Robinson, PhD, JD | Global Program Lead |
| Kevin Chin, MD, MS | Global Head, Early Clinical Development Immuno-Oncology |
| Philippe Serrano, PhD | Global Head, Regulatory Affairs Oncology |
| Jennifer Stevens, JD | Global Program Lead, Regulatory |
| Michael Bui, DDS, MPH, JD | Global Regulatory Affairs |
| Joleen White, PhD | Global Early Development |

| | |
|----------------------------------|---|
| Galit Rosen, MD | Medical Lead |
| Armin Schueler, PhD | Director, Global Biostatistics Oncology |
| Helga Koch, PhD | Global Drug Safety |
| Achta Paraiso Le Bourhis, PharmD | Regulatory CMC |
| Philip Witman, MPH, MPhil | Worldwide Safety and Regulatory, Oncology |
| Andy Blake-Haskins, PharmD | Asset Team Lead, Avelumab |

1.0 BACKGROUND

This pre-BLA meeting is for avelumab for the treatment of patients with locally advanced or metastatic UC whose disease has progressed (b) (4)

(b) (4). Anticipated BLA submission timeframe is December 2016/January 2017. This BLA will be based on data from the interim analysis of two combined UC cohorts from the large ongoing global Phase 1b open-label, dose-escalation study with concurrent parallel-group expansion in selected tumor types (EMR100070-001) conducted under IND 115747. The subjects from the combined cohorts: one N=44 subjects (“secondary expansion cohort”) and the other N=200 (“efficacy expansion cohort”) will serve as the pivotal population.

The primary analysis population in the efficacy expansion cohort as introduced in the Statistical Analysis Plan (SAP) (version 7, April 29, 2016) was the PD-L1 positive full analysis set (FAS) followed by patients in the FAS regardless of PD-L1 status. Similar efficacy was observed for PD-L1 positive and PD-L1 negative subjects in the efficacy expansion cohort (N=109). Therefore, the final analysis includes efficacy data from both cohorts. These cohorts had identical inclusion and exclusion criteria as well as identical response evaluation by the Independent Endpoint Review Committee (IERC). This study investigates the two UC cohorts (N=153) for anti-tumor activity in terms of best overall response (BOR) as assessed by IERC given a minimum 6 months of follow-up. Interim analyses were performed according to SAP version 7 at 4 and 6 months after the first dose date of the last subject of the 109 subjects enrolled in the efficacy expansion cohort.

Regulatory Background:

IND 115747 (EMD Serono as the Sponsor)

- December 23, 2015: The Sponsor submitted a Preliminary Breakthrough Therapy Designation (BTD) Request Advice describing preliminary results from the secondary expansion cohort of study EMR100070-001 (N=44 subjects with minimum 10 months of follow-up) in subjects with metastatic UC with positive PD-L1 expression.
- January 27, 2016: The Sponsor had a BTD advice teleconference wherein the Agency requested that the Sponsor submit data from an additional 25 to 35 subjects with metastatic or locally advanced UC with positive PD-L1 expression.
- June 9, 2016: FDA was provided with an update on the secondary expansion cohort of 44 subjects as well as data on an efficacy cohort of UC subjects according to a planned interim analysis (N=109 with 6 months of follow-up including 42 subjects with PD-L1+

tumors, and N=197 in the safety analysis set); the Sponsor was asked to submit a formal request for a pre-BLA meeting.

IND ^{(b) (4)} Pfizer as the Sponsor)

-  (b) (4)
- 

The clinical package for this BLA will be comprised of study reports from three ongoing studies (EMR100070-001 for treatment of various solid tumors (including the UC cohorts), EMR100070-002 for treatment of gastric cancer in Japanese subjects, and EMR100070-003 for treatment of metastatic Merkel cell carcinoma [mMCC]). Concurrently, EMD Serono is submitting a BLA to DOP2 (on a rolling basis) for avelumab for the treatment of mMCC (BLA 761049) and is seeking accelerated approval for that indication. The initial component of the mMCC BLA was submitted in July 2016 and the Sponsor expects the submission to be completed in September 2016. The content of the CMC sections of the eCTD for the UC BLA (Modules 2.3 and 3) will be identical to those contained in the mMCC submission. The nonclinical pharmacology and toxicology sections of the eCTD (Modules 2.4, 2.6, and Module 4) will be nearly identical to those contained in the mMCC BLA, differing only in the addition of UC-specific safety data within the exposure/safety analyses. Therefore, EMD Serono is requesting to cross-reference these modules of the mMCC BLA to support the BLA for UC.

The mMCC and UC BLAs also share a common source for the majority of their integrated safety analyses, i.e., study EMD100070-001. As of the November 20, 2015, cutoff date, 1452 subjects had been treated with at least one dose of avelumab in EMR100070-001. The data from study EMR100070-001 (November 20, 2015, cutoff date) will be used as the basis for the integrated safety analyses for the UC submission, together with the safety data from study EMR100070-003 (cutoff date of March 3, 2016) and the UC-specific safety data (cutoff date March 19, 2016). The mMCC BLA used this pooled safety dataset as the basis for its safety analyses, and the Sponsor proposes to use the same dataset in the UCC submission.

Topline efficacy results on the 153 UC subjects with at least 6 months of follow-up in study EMR100070-001 demonstrate a confirmed IERC-assessed ORR of 17.6% (95% CI: 12.0, 24.6%). The 24-week K-M rate of response durability was 92.0% (median duration not reached).

Safety results for subjects from the UC cohorts, as well as for all 1,540 subjects (all tumor types) in studies EMR100070-001 and EMR100070-003, are as follows; >90% of subjects had at least one TEAE, approximately 40% had SAEs, and 10% had TEAEs leading to death (mostly related to disease progression). Treatment-related Grade ≥ 3 TEAEs occurred in 7% of subjects in the UC cohorts, and in 9.7% of all subjects in studies EMR100070-001 and EMR100070-003.

Among the 1,540 subjects, 6 died from a TEAE related to avelumab therapy; one was in the UC efficacy expansion cohort (pneumonitis in a 54 year old male subject after 1 infusion of avelumab). IrAEs (Grade ≥ 3 irAEs) were reported in 20.5% (2.3%) and 12.2% (3.0%) of the secondary and efficacy expansion cohorts, respectively, and in 11.6% (1.6%) in all subjects of studies EMR100070-001 and EMR 100070-003.

FDA sent Preliminary Comments to EMD Serono on September 29, 2016.

2. DISCUSSION

2.1. Questions and Responses

Question 1: Does the Agency agree that the data from 153 subjects in the UC cohorts of Study EMR100070-001 with a minimum of 6 months of follow-up at the proposed cutoff date of March 19, 2016, together with a safety database consisting of more than 1500 subjects (further described in the briefing document) are sufficient to support the submission of a marketing application for the proposed indication under the accelerated approval provisions of 21 CFR 601 subpart E?

FDA Response: No. Your proposed indication is: Avelumab is indicated for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) whose disease has progressed during or after treatment (b) (4)

(b) (4)

You have treated 241 patients with urothelial cancer, but plan to present efficacy data for 153 patients. Please present efficacy data for all patients who have undergone at least one assessment at the time of data cutoff. Please use the data cutoff, for safety and efficacy, of June 2016, for patients with UC.

Among the 241 patients, 234 had received prior platinum-based therapy and seven were platinum-naïve (Table 6 of briefing book). These seven patients are insufficient to establish efficacy (b) (4) **Please revise your indication to** (b) (4)

While the number of patients available for the evaluation of efficacy in patients who have received a platinum-based regimen is relatively small, it is likely to be sufficient for filing, given the poor prognosis of the study disease and limited therapies for the disease. Whether this data will be sufficient for approval will be a review issue.

Given the small number of patients with urothelial cancer, we are concerned that the cutoff date for Study EMR100070-001, N=1294, is November 20, 2015. The Safety Update for this study will use a cutoff of June 9, 2016. Please explain your reason for the November 2015 cutoff. Please comment on whether data from the June 2016 cutoff can be included in the initial submission, along with the safety and efficacy data for the UC cohorts with the

June 2016 cutoff as requested above. Delayed submission of a substantial amount of data will impact the timelines for our review.

Most of the information in your safety database will come from a Phase 1 study and we are concerned about the duration of treatment (median 11.9 weeks). This will be a review issue.

EMD Serono's Response: EMD Serono acknowledges the FDA's feedback both on the indication proposed for the BLA and the data proposed to support a submission for accelerated approval under 21 CFR 601 Subpart E.

With regard to the indication:

We agree to modify the proposed indication to (b) (4)

With regard to including the safety data from the June 09, 2016 cut-off to support the BLA submission:

We understand FDA's concern with using the November 20, 2015 safety cut-off for safety data from subjects with underlying cancer disease other than UC supporting the BLA. After review, we agree to include safety data from the June 9, 2016 safety cutoff for both subjects with UC and other subjects and would like to discuss and obtain FDA's agreement as to how these data may be incorporated into the submission.

With regard to FDA's request to present efficacy data from all patients that had at least one assessment as of the cutoff date of June 9, 2016:

We agree with FDA's request to present efficacy data on all subjects that had at least one post-baseline tumor assessment as of the cutoff date of June 09, 2016. We would like to discuss and obtain FDA's agreement as to the timing and format of the presentation of these data.

Meeting Discussion: The use of a June 2016 cutoff in the SCS along with supportive data sets, and all narratives (UC and Non UC) up to June 2016 is acceptable. The narratives and CRFs will be included in the CSR addendums/appendix. The data cutoff will be included as part of the title for the adverse event data sets.

The proposal for the safety update, to update only the UC data, is acceptable. Please note that we may have additional questions and require additional data (such as cardiac events) during the review.

The Agency agrees to the submission of an efficacy update within 30 days of submission of the BLA that contains data on all 249 patients. This efficacy update will include revised data sets and revised tables and listings which contain all 249 patients based on the June 09, 2016, cut off. This information will be contained in the CO and SCE.

Question 2: Given that the BLA will be based on the results of two cohorts from a single Phase 1b open label study (EMR100070-001) and that the analyses from this limited dataset will fit within the Summary of Clinical Efficacy (SCE) in Module 2.7.3, does the Agency agree that the SCE can satisfy the requirement for the Integrated Summary of Efficacy (ISE) and that no separate ISE is necessary?

FDA Response: Yes.

EMD Serono's Response: EMD Serono acknowledges the FDA's feedback. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 3: Safety data from subjects on all tumor type cohorts from Study EMR100070-001 without UC subjects (N = 1294) and Study EMR100070-003 (N=88), in addition to safety data from subjects in the two UC cohorts (N = 44 + 197 = 241) will be included in the safety analyses. The analyses for the ISS are specified in the ISS statistical analysis plan (SAP). Does the Agency agree with the proposed cut-off dates, pooling strategy, definitions of irAEs and IRRs, and analyses described in the ISS SAP?

FDA Response: Your approach appears acceptable. Please see response to Question 1 concerning the cutoff dates.

Please include a flag for patients in the UC cohorts of study EMR100070-001 in the integrated safety datasets.

EMD Serono's Response: EMD Serono acknowledges the FDA's feedback, and agrees to flag the patients in the UC cohorts of study EMR100070-001 in the integrated safety datasets. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 4: EMD Serono and its partner, Pfizer, are currently conducting studies in a number of indications in addition to UC. Safety data from these various ongoing studies will not be included in the integrated safety data package (other than the integrated safety analyses from Studies EMR100070-001 and EMR100070-003). However, EMD Serono plans to submit serious adverse events (SAEs including SUSARs from all other studies from the Global Drug Safety Database and to summarize these data within the SCS/ISS separately from data for the UC cohorts and integrated safety analyses from Study EMR100070-001 and EMR100070-003. Does the Agency agree with the proposed presentation of safety data?

FDA Response: Yes.

EMD Serono's Response: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 5: Since the scope of the pooled safety dataset can fit within the Summary of Clinical Safety (SCS), safety analyses will be summarized in the SCS in Module 2.7.4, and supporting tables, listings, figures, and datasets will be in the ISS in Module 5.3.5.3. Does the Agency agree with this approach?

FDA Response: Yes.

EMD Serono's Response: EMD Serono acknowledges the FDA's feedback. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 6: Does the Agency agree with the proposed integrated analyses cutoff date of the postsubmission safety update report? We propose a 90-day safety update if Priority Review is granted.

FDA Response: See response to Question 1.**A decision concerning priority or standard review will be made at the time of filing.**

EMD Serono's Response: EMD Serono acknowledges the FDA's feedback. No further discussion is required.

Based on the FDA's preliminary comments, EMD Serono proposes to use a data cutoff date of June 9, 2016 for the ISS/SCS. Data for UC subjects, non-UC subjects and all subjects will be presented in parallel in the ISS/SCS. The number of subjects per group is included in the table below and amounts to N=249 in the UC subject group and to N=1489 in the non-UC subject group. The median treatment duration is 12.0 weeks for both groups and reflects the disease stage of the study population (locally advanced or metastatic cancer patients). The majority of subjects in both groups (> 90 %) had received their first study treatment more than 3 months prior to the data cutoff (June 9, 2016); and the median follow-up time amounted to 43.0 weeks (interquartile range 18.6; 52.6).

| | <i>UC subjects EMR 100070-001</i> | <i>Non-UC subjects EMR 100070-001 and EMR 100070-003</i> | <i>All subjects EMR 100070-001 and EMR 100070-003</i> |
|---|---------------------------------------|--|---|
| <i>Number of subjects</i> | <i>N=249</i> | <i>N=1489</i> | <i>N= 1738</i> |
| <i>Data cutoff</i> | <i>09Jun2016</i> | | |
| <i>Median treatment duration and interquartile range (weeks)</i> | <i>12.0 (6.0; 19.7)</i> | <i>12.0 (6.0; 26.0)</i> | <i>12.0 (6.0; 24.1)</i> |
| <i>Number and % of subjects with > 3 months follow-up time</i> | <i>235 (94.4)</i> | <i>1454 (97.6)</i> | <i>1689 (97.2)</i> |

In addition to data from the clinical database as outlined above, EMD Serono will supplement the safety data with serious adverse event data from the Global Drug Safety Database from the data cutoff of June 9, 2016 through September 30, 2016. For all other ongoing clinical trials sponsored by EMD Serono or Pfizer, all SAEs cumulatively through September 30, 2016 will be provided.

In terms of the Safety Update Report (SUR), the report is proposed to be submitted 3 months after the submission of the initial BLA in January 2017 (90 day safety update report), if the FDA grants priority review for the BLA. EMD Serono proposes to submit updated data for all UC subjects using a data cutoff of September 30, 2016. Any new safety information that may affect the labeling will be submitted including exposure, adverse event and laboratory data. In addition to data from the clinical database, serious adverse event data from the Global Drug Safety Database for the period of October 1, 2016 to January 31, 2017 for all ongoing studies will be provided.

Meeting Discussion: No discussion took place at the meeting.

Question 7: EMD Serono proposes to submit a complete CDISC data package that supports the safety and efficacy of avelumab, more specifically data from Study EMR100070-001, and to report laboratory data, including tables, listings, and figures, in Système International (SI) units only, rather than in SI and U.S. conventional units. The package will be supplemented by the ADaM datasets of the ISS which also includes U.S. conventional units. Does the Agency agree with the proposed data package?

FDA Response: Yes. Please submit the labs referenced in Table 27 (Lab Parameters in SI and US Conventional Units) in the integrated datasets.

EMD Serono's Response: EMD Serono acknowledges the FDA feedback, and agrees to submit the labs referenced in Table 27 (Lab Parameters in SI and US Conventional Units) in the integrated datasets. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 8: Does the Agency agree with the narrative plan and plan for submission of CRFs for the Study EMR100070-001 UC cohort interim analysis CSR, and the respective CSRs for Studies EMR10070-001, - 002 and -003?

FDA Response: Yes.

EMD Serono's Response: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 9: The Clinical Pharmacology package described in the briefing document will be included with the BLA. Does the Agency agree that the proposed clinical pharmacology package is sufficient to support the submission of a BLA for UC?

FDA Response: The proposed clinical pharmacology package appears acceptable to support the BLA submission. The adequacy of the data will be evaluated at the time of the BLA review.

EMD Serono's Response: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 10: The proposed nonclinical pharmacology and toxicology package is nearly identical (with the exception of added UC-specific safety data) and the CMC package is identical to the packages being submitted in support of BLA No. 761049 (for mMCC). We propose to cross-reference the nonclinical pharmacology and toxicology sections of BLA No. 761049 to support our BLA for the UC indication. The nonclinical package was submitted to DOP2 on July 6, 2016. The CMC package (described in the briefing document) will be submitted to DOP2 in September 2016 to support BLA No. 761049 for the mMCC indication. Does the Agency agree that we may cross-reference the nonclinical pharmacology and toxicology sections (Modules 2.4, 2.6, and 4) of the mMCC BLA No. 761049 nonclinical package to support the BLA for UC? Does the Agency agree that the nonclinical package is sufficient to support the submission of a BLA for UC?

FDA Response: Your approach to cross-reference the nonclinical pharmacology and toxicology sections of BLA 761049 to support your BLA for the UC indication is acceptable. The nonclinical package appears to be sufficient to support the submission of a BLA for the proposed UC indication; however, the final decision on the adequacy of the nonclinical data to support approval of a BLA for the proposed indication will be determined following our review of your BLA submission.

EMD Serono's Response: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

Question 11: Does the Agency also agree that EMD Serono may cross-reference the CMC package (Modules 2.3 (Quality Overall Summary) and 3 (Quality)) of the mMCC BLA submission?

FDA Response: Yes, we agree.

EMD Serono's Response: EMD Serono acknowledges the FDA feedback. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

(b) (4)

Additional comments:

- 1. Please flag patients treated beyond RECIST v1.1-defined PD in the efficacy datasets.**

EMD Serono's Response: EMD Serono acknowledges the FDA's feedback, and agrees to flag patients treated beyond RECIST v1.1-defined PD in the efficacy datasets.

- 2. Please comment on the possible reasons for the difference in the response rate in PD-L1 positive/negative patients in the secondary expansion cohort, but not in the efficacy expansion cohort.**

EMD Serono's Response: Currently, the prognostic value of PD-L1 expression in subjects with UC is unknown. Furthermore, the clinical utility of PD-L1 testing to predict subjects more likely to respond to anti-PD-L1 has yet to be confirmed. Although the secondary expansion cohort (N=44) indicated a trend towards higher response rate in PD-L1 positive subjects, a similar trend was not observed in the efficacy expansion cohort (N=109). One explanation for the difference in response rate is small sample size, however, both the secondary and efficacy expansion cohorts had identical inclusion/exclusion criteria and demographic data showing that the two overall patient populations to be relatively similar. EMD Serono is continuing to explore this topic and will provide additional comment in the BLA submission.

3. In the package, you should provide the SAS program used to derive the response status from raw data (target lesion measurements, non-target status, and new lesion status at each assessment) following RECIST v1.1 based on investigator and central radiology assessments. This program should be stand-alone (i.e., no macros) so that it can be run on FDA computers. Please also submit an output dataset (one record per patient per tumor assessment) including the following data:
 - Patient ID, Randomized arm, Visit number, Visit name, Visit date, Baseline target lesion SLD, Target lesion SLD at this visit, % change of SLD from baseline, Nadir SLD value, % change of SLD from nadir, Non-target lesion response status at this visit, New lesion (yes/no) at this visit, Response status at this visit, Best overall response, Confirmed response (yes/no), Evaluator (Investigator or Central radiology)

EMD Serono's Response: Agree. No further discussion is required.

Meeting Discussion: No discussion took place at the meeting.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

The Agency agrees that a June 2016 cutoff data for safety information will be used only in the Summary of Clinical Safety and that supportive data sets will be provided.

The Agency agrees that narratives (urothelial cancer and non-urothelial cancer), and the accompanying case report forms, for events that occurred between the cutoff dates for the clinical study reports (CSR) and June 2016 will be included in a CSR addendums/appendix.

The Agency agrees that Safety Update will be limited to additional data in patients with urothelial cancer.

The Agency agrees to the submission of an efficacy update within 30 days of submission of the BLA that contains data on all 249 patients. This efficacy update will include revised data sets and revised tables and listings which contain all 249 patients based on the June 9, 2016, cut off. The Agency agrees that this information will only be contained in the Clinical Overview and Summary of Clinical Efficacy.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

The Agency agrees to the submission of an efficacy update within 30 days of submission of the BLA that contains data on all 249 patients. This efficacy update will include revised data sets and revised tables and listings which contain all 249 patients based on the June 9, 2016, cut off.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - CLINICAL

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). 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 related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

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).

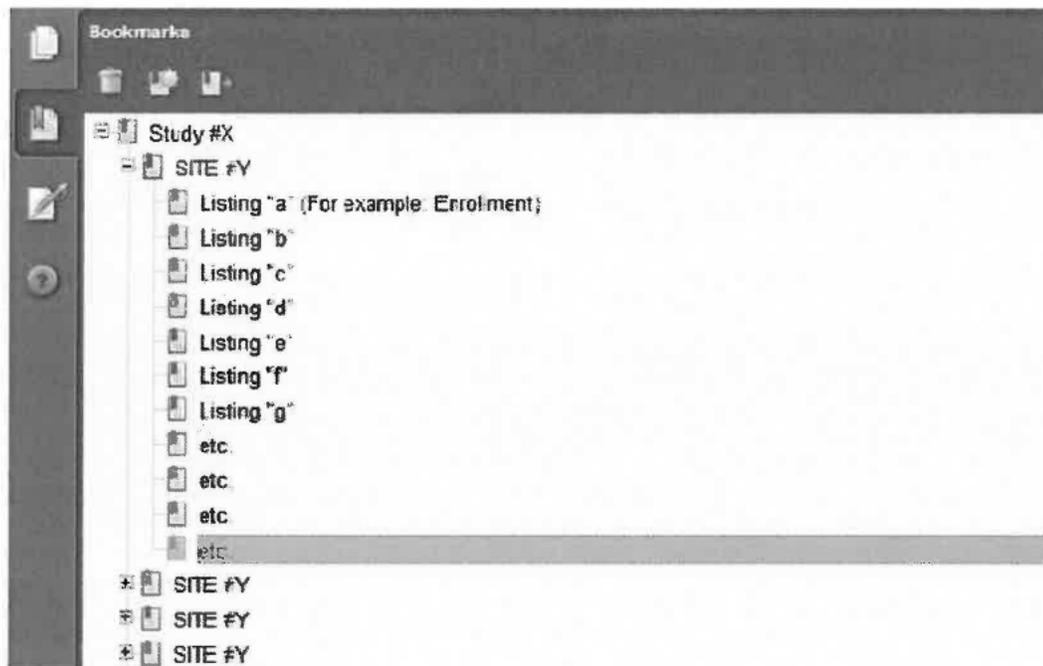
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - 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

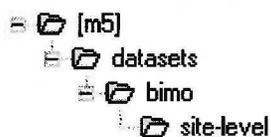
Technical Instructions:

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 Item ¹ | 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues require further discussion.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

See attached.

12 Page(s) have 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/

CHARLENE N WHEELER
10/17/2016

VIRGINIA E MAHER
10/17/2016

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 761078

LATE-CYCLE MEETING MINUTES

EMD Serono, Inc.
Attention: Jennifer Stevens, JD
Global Regulatory Program Lead, Immuno-Oncology
One Technology Place
Rockland, MA 02370

Dear Ms. Stevens:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Bavencio™ (avelumab), Intravenous, 200 mg/10 mL (20 mg/mL) in a single-dose vial.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on April 7, 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 Kim J. Robertson, Regulatory Health Project Manager at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

V. Ellen Maher, MD
Clinical Team Leader
Division of Oncology Products 1
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: April 7, 2017; 3:00pm EST
Meeting Location: Teleconference

Application Number: BLA 761078
Product Name: Bavencio™ (avelumab) Injection
Applicant Name: EMD Serono, Inc.

Meeting Chair: V. Ellen Maher, MD
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES:

Geoffrey Kim, MD, Director, DOP1
Julia Beaver, MD, Acting Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
V. Ellen Maher, MD, Clinical Team Leader, DOP1
Chana Weinstock, MD, Clinical Reviewer, DOP1
Joyce Cheng, PhD, Biometrics Reviewer, DBV
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Wei Chen, PhD, Nonclinical Reviewer, DHOT
Nan Zheng, PhD, Clinical Pharmacology Reviewer, DPM
Jingyu (Jerry) Yu, PhD, Clinical Team Leader, DPM
Frances Fahnbulleh, PharmD, RPh, Project Manager, OSE
Kim J. Robertson, Regulatory Health Project Manager, DOP1

EMD SERONO, INC./PFIZER/MERCK KGaA ATTENDEES:

Kevin Chin, MD, Vice President, Immuno-Oncology, EMD Serono
Galit Rosen, MD, Medical Director, Immuno-Oncology, EMD Serono
Marcis Bajars, MD, Medical Director, Immuno-Oncology, Merck KGaA
Jacques Mascaro, PhD, Sr. VP, Head of Global Regulatory Affairs & R&D Quality
Jennifer Stevens, JD, Global Regulatory Prog Lead, Immuno-Oncology, EMD Serono
Philippe Serrano, PhD, Head of Regulatory Immuno-Oncology/Oncology, EMD Serono
Junyuan Julia Xiong, MS, Assoc Director, Global Biostatistics, EMD Serono
Helga Koch, PhD, Director, Global Drug Safety, Merck KGaA
Joleen White, PhD, Assoc Director, Global Early Development, EMD Serono
Yulia Vugmeyster, PhD, Clinical Pharmacologist, EMD Serono
Stefanie Fischer, Principal Clinical Data Sciences, Merck KGaA
Dagmar Kottig-Roth, PhD, Senior Data Standards and Governance Mgr, Merck KGaA
Michael Bui, DDS, JD, MPH Director, Global Regulatory Affairs
Christian Wrehlke, PhD, MDRA, Assoc Director, Labeling

Shannon Dauksis, PharmD, PMP, R&D Project Manager
Laurie Strawn, PhD, Pfizer, Global Reg Portfolio Lead, Immuno-Onc./GU Malignancies
Glen Andrews Pfizer, Asset Team Lead

1.0 BACKGROUND

BLA 761078 was submitted on December 27, 2016 for Bavencio™ (avelumab), Intravenous, 200 mg/10 mL (20 mg/mL) in a single-dose vial.

Proposed indication(s): Advanced or metastatic urothelial carcinoma with disease progression on or after platinum-based therapy

PDUFA goal date: August 27, 2017

FDA issued a Background Package in preparation for this meeting on April 6, 2017.

2.0 DISCUSSION

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

- The Agency recommends that the EMD Serono, Inc. optimize the dose of avelumab and notes that this may lead to a higher response rate in urothelial cancer. We plan to request a post-marketing commitment (PMC) to submit the results of the ongoing trial (EMR100070-005) in patients with non-small cell lung cancer (NSCLC). It is the Applicant's choice whether to start a dose optimization trial in urothelial cancer.
- There will be a PMR for the ongoing confirmatory study. The confirmatory study includes monitoring of the following: thyroid function, amylase/lipase, troponin, and collection of adverse events 90 days after the last dose of avelumab. These issues were not fully addressed in the Phase 1 study.
- Additional PMCs may be needed.
- We plan to include the confirmed response rate prior to the cutoff date in patients with ≥ 24 weeks (6 months) and ≥ 13 weeks of follow up in the package insert.
- The review of issues with the PD-L1 assay is ongoing.

Discussion: The Agency reiterated the bulleted Substantive Issues with EMD Serono and recommended that they optimize the dose of avelumab in urothelial cancer.

The Agency informed EMD Serono that it intended to send labeling to them following the conclusion of the Late Cycle Meeting.

Discussion: The Agency confirmed that there was no need to take this application to an Advisory Committee meeting.

LCM AGENDA

1. Introductory Comments – ~5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

Discussion: The discussion of all Substantive Issues DOP1 had were outlined and discussed. See above.

3. Information Requests

Discussion: Additional requests for information could be forthcoming, as the review of the application is still ongoing. To date, EMD Serono, Inc. has addressed all outstanding information requests.

4. Discussion of Upcoming Advisory Committee Meeting

Discussion: The Agency informed EMD Serono that there were no plans to take the avelumab application to an Advisory Committee Meeting.

5. Postmarketing Requirements/Postmarketing Commitments

Discussion: The applicant was made aware that potential PMRs and PMCs were forthcoming, once they were finalized.

6. Review Plans

Discussion: EMD Serono was told that DOP1 will continue with the review of the application and provide the applicant with requests for information if needed, until the final regulatory action is taken.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

VIRGINIA E MAHER
05/03/2017

Robertson, Kim

From: Robertson, Kim
Sent: Thursday, April 06, 2017 4:32 PM
To: 'Jennifer Stevens'
Subject: RE: BLA 761078; avelumab---Late Cycle Meeting

Dear Jennifer:

Please note that it *might* be necessary for us to move our Late Cycle Meeting t-con's start time from 3:00pm EST to **3:30pm EST**. Whether we begin at 3pm, or 3:30pm, I ask that EMD stands by and gives us the 30 minutes allowance, in case we need to start it a little later. A 30 minutes window for discussions however, should still be sufficient.

Regards,
Kim

Kim J. Robertson
Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [mailto:jennifer.stevens@emdserono.com]
Sent: Thursday, April 06, 2017 12:38 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Late Cycle Meeting

Hi Kim – Thank you very much for this information. Do you have an idea when we might expect to see labeling – or will this be discussed tomorrow? Regards, Jennifer

From: Robertson, Kim [mailto:Kim.Robertson@fda.hhs.gov]
Sent: Thursday, April 06, 2017 6:35 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Late Cycle Meeting
Importance: High

Dear Jennifer:

Please see the attached .pdf document, as it is the LCM Background Document that contains a brief overview of the agenda of our discussion items. I believe it will address some of your bulleted items below.

Relative to the question as to how the BLA will be maintained and communications going forward, I am told that since DOP2 approved their application first, DOP1's BLA (if approved), would be integrated into DOP2's, and DOP1's BLA would be administratively closed.

Regards,
Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441
kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Wednesday, April 05, 2017 5:33 AM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Late Cycle Meeting

Dear Kim –

There are several things that we might discuss at the Late Cycle meeting, again somewhat depending upon what FDA records on the agenda. These would be -

- We would like to confirm that FDA has no significant review issues and to understand whether FDA anticipates additional IRs for EMD.
- We would like to confirm that submission of the results of EMR100070-005 upon completion is the only PMC or -- if FDA has other expectations on PMRs/PMCs – to align on any such PMC/PMR.
- We would like to discuss labeling (or there may be no need, depending upon the mark-up that we will receive back from you) and to understand FDA's thoughts on the combine
- We would like to discuss if/how the 2 BLAs are to be maintained/combined and appropriate communication with one/both divisions moving forward, assuming this BLA is approved.
- We would like to have a sense of FDA's timing and/or to understand any implications of an approval of a competitor which we understand is fairly imminent.

Thanks very much for your help. If easier to discuss, please feel free to call my mobile at [REDACTED] (b) (6).

Regards, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Tuesday, April 04, 2017 7:48 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: RE: BLA 761078; avelumab---Late Cycle Meeting

Dear Jennifer:

Relative to the Late Cycle Meeting, does EMD have any matters/issues/concerns that it would like to discuss with the Division, given that EMD would like to proceed with the t-con?

Pertinent to labeling, it is possible that we might be able to convey labeling to EMD. We have an internal labeling meeting tomorrow, so upon the conclusion of that meeting, we will determine if labeling can be conveyed to EMD.

Lastly, I responded directly to your e-mail that addressed our clinical IR.

Regards,
~Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration
Tel: 301-796-1441

kim.robertson@fda.hhs.gov



From: Jennifer Stevens [<mailto:jennifer.stevens@emdserono.com>]
Sent: Tuesday, April 04, 2017 12:14 PM
To: Robertson, Kim
Subject: RE: BLA 761078; avelumab---Late Cycle Meeting

Hi Kim –

Apologies for the slightly late reply. I am in Europe and having some connection issues. EMD would like to proceed with the meeting. Could you confirm whether FDA will be sending the draft labeling tomorrow as outlined in the filing letter?

If I might, could I please also request that you confirm receipt of the IR Response on measuring PD-L1 expression that I sent to you early today?

Thank you and best regards, Jennifer

From: Robertson, Kim [<mailto:Kim.Robertson@fda.hhs.gov>]
Sent: Friday, March 31, 2017 9:28 PM
To: Jennifer Stevens <jennifer.stevens@emdserono.com>
Subject: BLA 761078; avelumab---Late Cycle Meeting
Importance: High

Dear Jennifer:

This is just a reminder from the Mid Cycle Communication Meeting, that the Late Cycle Meeting scheduled for this BLA is slated for **Friday, April 7, 2017, 3:00pm-3:30pm EST.**

Should EMD Serono decide to hold this t-con, you may use the following call-in information:

Local: 1-301-796-7777

Toll free: 1-855-828-1770

Cisco Unified MeetingPlace meeting ID: (b) (4)

Alternatively, EMD Serono has the option of cancelling this meeting, given that EMD and DOP1 have been in continuous communications with one another during the designated review cycle.

Please let me know by Tuesday, April 4, 10:00am EST if EMD desires to proceed with a Late Cycle Meeting.

Regards,

Kim

Kim J. Robertson

Regulatory Health Project Manager

Division of Oncology Products 1
Office of Oncology and Hematology Products
Center for Drugs and Evaluation Research
U.S. Food and Drug Administration

Tel: 301-796-1441

kim.robertson@fda.hhs.gov



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/s/

KIM J ROBERTSON
04/06/2017



BLA 761078

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

EMD Serono, Inc.
Attention: Jennifer Stevens, JD
Global Regulatory Program Lead, Immuno-Oncology
One Technology Place
Rockland, MA 02370

Dear Ms. Stevens:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for Bavencio™ (avelumab), Intravenous, 20mg/mL, 10 mg/kg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for April 7, 2017. Attached is our background package, including our agenda, for this meeting.

Please email me a list of your attendees at kim.robertson@fda.hhs.gov, at least one week prior to the meeting.

If you have any questions, call Kim J. Robertson, Regulatory Health Project Manager, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Geoffrey Kim, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug and Evaluation Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: April 7, 2017, 3:00pm – 3:30pm
Meeting Location: Teleconference

Application Number: BLA 761078
Product Name: Bavencio™ (avelumab)
Indication: Advanced or metastatic urothelial cancer
Applicant Name: EMD Serono, Inc.

FDA ATTENDEES (tentative)

Geoffrey Kim, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Julia Beaver, MD, Associate Director, DOP1
V. Ellen Maher, MD, Clinical Team Leader, DOP1
Chana Weinstock, MD, Clinical Reviewer, DOP1
Joyce Cheng, PhD, Biometrics Reviewer, DBV
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Wei Chen, PhD, Non Clinical Reviewer, DHOT
Todd Palmby, PhD, Non Clinical Reviewer, DHOT
Nan Zheng, PhD, Clinical Pharmacology Reviewer, DPM
Jingyu (Jerry) Yu, PhD, Clinical Pharmacology Team Leader, DPM
Kim J. Robertson, Regulatory Health Project Manager, DOP1

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.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

- The Agency recommends that the EMD Serono, Inc. optimizes the dose of avelumab and notes that this may lead to a higher response rate in urothelial cancer. We plan to request a post-marketing commitment (PMC) to evaluate the efficacy and safety of BAVENCIO™ at a higher dose, or a more frequent dose in patients with urothelial cancer (UC), depending on the results of the ongoing trial (EMR100070-005) in patients with non-small cell lung cancer (NSCLC). It is the applicant's choice however, to determine whether to start the dosing optimization trial after the results of the ongoing trial (EMR100070-005) are available.
- There will be a PMR for the ongoing confirmatory study. The confirmatory study includes monitoring of the following: thyroid function, amylase/lipase, troponin, and collection of adverse events 90 days after the last dose of avelumab. These issues were not fully addressed in the Phase 1 study.
- Additional PMCs may be needed.
- We plan to include the confirmed response rate prior to the cutoff date in patients with ≥ 24 weeks and ≥ 13 weeks of follow up in the package insert.
- The review of issues with the PD-L1 assay is ongoing.

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.

LCM AGENDA

1. Introductory Comments – ~5 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – ~15 minutes

3. Discussion of Minor Review Issues – 0 minutes
N/A
4. Additional Applicant Data – It is possible that the need for additional data may be necessary; however, this may be determined either during the Late Cycle discussions, or before the regulatory action is taken.
5. Information Requests – Additional requests for information could be forthcoming, as the review of the application is still ongoing. To date, EMD Serono, Inc. has addressed all outstanding information requests.
6. Discussion of Upcoming Advisory Committee Meeting – 0 minutes
7. REMS or Other Risk Management Actions – 0 minutes
8. Postmarketing Requirements/Postmarketing Commitments – ~5-10 minutes
9. Major labeling issues -0 minutes
10. Review Plans – 0 minutes
DOP1 will continue with the review of the application and provide the applicant with requests for information if needed, until the final regulatory action is taken.
11. Wrap-up and Action Items – 0 minutes

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/s/

GEOFFREY S KIM
04/06/2017