CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Memo

BLA Number	761049 (SDNs 4, 8, 9, 17, 22 and 32)
Link to EDR	\\CDSESUB1\evsprod\BLA761049\761049.enx
Submission Dates	9/23/2016 (SDN 4), 10/27/2016 (SDN 8), 10/28/2016 (SDN 9), 12/13/2016 (SDN 17), 12/23/2016 (SDN 22), and 1/31/2017 (SDN 32)
Submission Type	Original BLA - Priority (rolling submission)
Brand Name	BAVENCIO
Generic Name	Avelumab (MSB0010718C)
Dosage Form and Strength	20 mg/mL solution in single-use vials
Route of Administration	Intravenous (IV) infusion over 60 minutes
Proposed Indication	Metastatic Merkel cell carcinoma (mMCC) whose disease has progressed after at least one previous chemotherapy regimen
Applicant	EMD Serono Inc.
Associated INDs	115747 (solid tumors), 119394 (MCC), (b) (4)
OCP Review Team	Safaa Burns, Ph.D; Nan Zheng, Ph.D; Jeanne Fourie Zirkelbach, Ph.D and Jiang Liu, Ph.D
OCP Final Signatory	Nam Atiqur Rahman, PhD, Division Director

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. The proposed dosing regimen of 10 mg/kg every two weeks administered by intravenous infusion over 60 minutes has demonstrated clinical efficacy with a tolerable safety profile; therefore the proposed dosing regimen is acceptable. From a Clinical Pharmacology standpoint, the BLA is acceptable to support approval provided that the Applicant and the FDA reach an agreement regarding the labeling language.

Refer to the multidisciplinary review in DARRTS for details.

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/s/

SAFAA BURNS
02/21/2017

NAN ZHENG
02/21/2017

JIANG LIU
02/21/2017

JEANNE FOURIE ZIRKELBACH
02/21/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

BLA Number	761049	**SDN**	4
Applicant	EMD Serono, Inc.	**Submission Date**	9/23/2016
Generic Name	Avelumab	**Brand Name**	BAVENCIO
Drug Class	A fully human IgG1 monoclonal antibody (mAb) directed against the PD-L1 molecule expressed on tumor cells as well as a number of immune cells		
Indication	Metastatic Merkel Cell Carcinoma (mMCC)		
Dosage Regimen	10 mg/kg Q2W		
Dosage Form	20 mg/ mL sterile solution in a single-dose glass vial	**Route of Administration**	intravenous (IV) infusion
OCP Division	DCPV	**OND Division**	DOP2

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Safaa Burns	Jeanne Fourie-Zirkelbach
Pharmacometrics	Nan Zheng	Jiang Liu
Genomics	Rosane Charlab Orbach	NA

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date (Day 60)	11/22/2016	**74-Day Letter Date**	12/6/2016
Review Due Date	2/23/2017	**PDUFA Goal Date**	5/23/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

If yes list comment(s): An IR pertaining to the popPK and E-R datasets was sent to EMD Serono on 10/14/2016.

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		1	Comparison of PK from Process A and Process B, pooled PK data from Studies EMR100070-001, -002 & -003
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose		Phase 1 Studies -001 and -002
	☑ Multiple Dose	3	Phase 1 Studies -001 and -002 Registration Phase 2 Study -003 (Part A only, as no patients had been enrolled yet into Part B at the time of data cutoff of 3/3/2016)
☐ Mass Balance Study			
☑ Other (e.g. dose proportionality)			Study -001
Intrinsic Factors			
☑ Race			PopPK analyses of pooled data from Studies -001, -002 & -003
☑ Sex			As above
☑ Geriatrics			As above
☐ Pediatrics			
☑ Hepatic Impairment			As above
☑ Renal Impairment			As above
☐ Genetics			
Extrinsic Factors			
☑ Effects on Primary Drug			PopPK analyses of pooled data from Studies -001, -002 & -003
☑ Effects of Primary Drug			As above
Pharmacodynamics			
☑ Healthy Subjects		1	*In vitro* biomarker study to measure targeted occupancy (TO) by spiking avelumab into whole blood samples from healthy volunteers
☑ Patients		1	*Ex vivo* biomarker study to measure TO in PBMCs in whole blood samples from patients enrolled in Study -001
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			

☑ QT	1	PopPK analyses of pooled data from Studies -001, -002 & -003
Pharmacometrics		
☑ Population Pharmacokinetics	1	PopPK analyses of pooled data from Studies -001, -002 & -003
☑ Exposure-Efficacy	1	As above
☑ Exposure-Safety	1	As above

Total Number of Studies	***In Vitro***	1	***In Vivo***	9
Total Number of Studies to be Reviewed		1		9

Criteria for Refusal to File (RTF)

RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	Comparability popPK analysis for data from drug product made of DS "A" and DS "B"
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	**PK Reports:** RF6870, RF7010, 218-1407 & 15-IV104-V0 **ADA Reports:** TNJS13-170, TNJS13-170A1, IP190 & IP373
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☑No ☐N/A	PopPK and E-R datasets were requested as an IR on 10/14/2016 and have to be submitted by 10/31/2016 to the current BLA submission.
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	

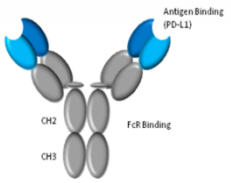
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☑No ☐N/A	PopPK and E-R datasets were requested as an IR on 10/14/2016 and have to be submitted by 10/31/2016 to the current BLA submission.
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Avelumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody (mAb) directed against programmed death ligand 1 (PD-L1) molecule. It consists of two heavy chains (HC) of 450 amino acid residues each and two light chains LC of 216 amino acid residues each with typical IgG1 inter and intra chain disulfide

bonds (see Applicant's **Figure 1**). The molecular mass of intact avelumab, calculated on the basis of the amino acid composition and predicted disulfide bonding without glycans is 144 KDa, the mass including glycans is approximately 147 KDa.

Figure 1: Structure of Avelumab



Mechanism of Action: Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors, Programmed Death 1 (PD-1) and B7.1. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T cells, resulting in the restoration of antitumor T cell responses.

Indication: The proposed indication is for the treatment of patients with metastatic Merkel Cell Carcinoma (mMCC) who have received at least one line of previous chemotherapy. mMCC is an aggressive skin cancer with no approved therapies and no evidence-based standard of care. mMCC is an associated with Merkel cell polyomavirus (MCV [or MCPyV]), exposure to ultraviolet irradiation, immunosuppression and advanced age.

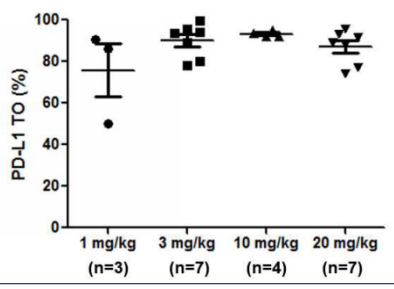
Drug Product: The drug product (DP) is a **200 mg/10 mL** (**20 mg/mL**) sterile solution in a single-dose glass vial intended for IV infusion following dilution. Initially, the DP was formulated at a protein concentration of (b) (4) using avelumab drug substance (DS) from the initial manufacturing process called **Process A** (b) (4) . This formulation (b) (4) was used throughout the early development program (Phase 1 clinical trials). To support future clinical development and commercial use, an optimized formulation of avelumab at higher concentration (**200 mg/10 mL**) was developed. This formulation was prepared using avelumab DS from a changed manufacturing process called **Process B**. The DP produced using **Process B** is being used in ongoing clinical trials and at initiation of all subsequent clinical trials and commercial supply. The popPK analysis of pooled PK data across Studies -001, -002 and -003 showed that there was no influence of the change in manufacturing process on the exposure to avelumab.

Proposed Recommended Dosage: The proposed recommended dose is 10 mg/kg administered as an intravenous infusion over 60 minutes once every 2 weeks (Q2W) until disease progression or unacceptable toxicity.

Justification for Recommended Dose

The proposed recommended dose of 10 mg/kg Q2W was selected based on adequate safety and tolerability obtained in the phase 1 dose-escalation Study -001 where doses of 1.0, 3.0, 10 and 20 mg/kg were studied with **no** MTD reached. Based on *ex vivo* data from Study -001 to evaluate PD-L1 Target Occupancy [**TO**] on circulating CD3+ T cells, a mean TO of 75.7±22.1% was observed prior to the second infusion on Day 15 in the 1 mg/kg cohort. In the 3 mg/kg cohort, the mean TO on Day 15 was 90±8.1%. A mean TO of 93.2 ± 1.3% was observed in 10 mg/kg cohort on Day 15, while the mean TO was 85±8.7% in the 20 mg/kg cohort on Day 15 (see Applicant's **Figure 6**).

Figure 6 Target Occupancy in 1, 3, 10, and 20 mg/kg Cohorts Assessed on Prior to the Second Avelumab Infusion



Registration Trial -003 (Part A): This is an ongoing phase 2 open-label, single-arm study to evaluate the efficacy and safety of avelumab in patients with mMCC who have received at least one line of previous chemotherapy. Patients were enrolled regardless of tumor PD-L1 or MCV status. The primary efficacy analysis was performed in the **88** mMCC patients who enrolled in Part A of the study at the proposed recommended dose of 10 mg/kg Q2W. As a cut-off date of **3/3/2016**, efficacy results from Part A are summarized in Applicant's **Table 3**.

Table 3: Efficacy Results of Study 003

Efficacy Endpoints (Tumor assessment per RECIST v1.1, IERC)	Results (N = 88)
Confirmed Best Overall Response (BOR)	
Complete Response (CR)* n (%)	8 (9.1%)
Partial Response (PR)* n (%)	20 (22.7%)
Objective Response Rate (ORR)	
Response Rate, CR+PR* n (%)	28 (31.8%)
(95.9% CI)[a]	(21.9, 43.1)
Duration of Response (DOR)[b]	
Median, months (95% CI)	NR (8.3, not estimated)
Minimum, Maximum	2.8+, 17.5+
≥ 6 months by K-M, (95% CI)	92% (70, 98)
Progression-free Survival (PFS)	
6-month PFS rate by K-M, (95% CI)	40% (29, 50)
Overall Survival (OS)	
6-month OS rate by K-M, (95% CI)	69% (58, 78)

CI: Confidence interval; RECIST: Response Evaluation Criteria in Solid Tumors; IERC: Independent Endpoint

Avelumab was associated with an objective response rate (ORR) of 32% (95.9% CI adjusting for group sequential testing: 21.9, 43.1).

Safety Results from Study 003 (Part A):
As a cutoff date of **3/3/2016**, the most common adverse reactions (≥ 20%) were fatigue, diarrhea, and nausea and were Grade 1 or 2 in severity. The most common Grade 3-4 adverse reactions (≥ 3%) were anemia, hypertension, lymphopenia, increased gamma-glutamyltransferase and increased lipase. Serious adverse reactions reported in ≥ 2% of patients were anemia, fatigue, and abdominal pain. Applicant's **Table 1** below described adverse reactions occurred in Study -003, in 88 MCC patients treated at 10 mg/kg Q2W dose.

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Table 1: All Grade Adverse Reactions in ≥ 10% of Patients with metastatic MCC i Study 003

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Adverse Reactions[1]	BAVENCIO (N = 88)	
	All grades toxicity (%)	Grade 3-4 toxicity (%)
Gastrointestinal Disorders		
Diarrhea	23	0
Nausea	21	0
Constipation	17	1
Abdominal pain[a]	16	2
Vomiting	11	0
General Disorders and Administration Site Conditions		
Fatigue[b]	50	2
Peripheral edema[c]	19	0
Injury, Poisoning and Procedural Complications		
Infusion related reaction[d]	17	0
Investigations		
Decreased weight	14	0
Metabolism and Nutrition Disorders		
Decreased appetite	19	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[e]	30	2
Arthralgia	16	1
Nervous System Disorders		
Dizziness	13	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	17	0
Skin and Subcutaneous Tissue Disorders		
Rash[f]	17	0
Vascular Disorders		
Hypertension	13	6

[1] MedDRA version 18.1

Clinical Pharmacology Studies: The clinical pharmacology of avelumab (including PK, PK/PD, QTc, and immunogenicity assessments) has been characterized in Studies -001, -002, and -003 (See Applicant's tables below).

Table 1 Overview of Pivotal Study in Metastatic Merkel Cell Carcinoma and Key Supportive Studies

Study No.	Study Design	Subject Population	No. of Subjects
Pivotal Study in mMCC			
EMR100070-003 Conducted in US, Australia, Austria, France, Germany, Italy, Japan, Spain, and Switzerland	Part A: Phase II, open-label, single-arm study Objectives: Efficacy, safety, biomarkers, PK Primary endpoint: Confirmed BOR per IERC	Part A: Adult subjects who have progressed after receiving at least 1 line of previous chemotherapy for the treatment of mMCC	Part A: 88 subjects (enrollment complete) 10 mg/kg every 2 weeks
	Part B: Phase II, open-label, single-arm study Objectives: Efficacy, safety, biomarkers, PK Primary endpoint: Durable response	Part B: Adult, systemic chemotherapy-naïve subjects with mMCC	Part B: at least 100 subjects planned 10 mg/kg every 2 weeks
Key Supportive Studies			

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EMR100070-001 Conducted in US, Belgium, Czech Republic, France, Germany, Hungary, Korea, Poland, Taiwan, Republic of China, and UK	Phase I, open-label, 2-phase (dose escalation and treatment expansions) in solid tumors Objectives: Safety/tolerability, MTD, efficacy (treatment expansion phase only), and PK	Adult subjects with metastatic or locally advanced solid tumors and expansion to selected indications	Dose escalation: 53 subjects (completed) 4 at 1 mg/kg, 13 at 3 mg/kg, 15 at 10 mg/kg, and 21 at 20 mg/kg every 2 weeks Dose expansion: (ongoing) 1437 subjects 10 mg/kg every 2 weeks
EMR100070-002 Conducted in Japan	Phase I, open-label, 2-phase (dose escalation and treatment expansion) in solid tumors Objectives: Safety/tolerability, MTD, efficacy, and PK	Adult subjects with metastatic or locally advanced solid tumors, with expansion in subjects with gastric cancer	Dose escalation: (completed) 17 subjects 5 at 3 mg/kg, 6 at 10 mg/kg, and 6 at 20 mg/kg every 2 weeks Dose expansion: (ongoing) 34 subjects 10 mg/kg every 2 weeks

As a cutoff date of **11/20/2015**, the PK of avelumab has been determined using both non-compartmental analyses (NCA) and PopPK analysis (see attached Applicant's **Table 4**). The results from the PopPK analysis are presented as follows:

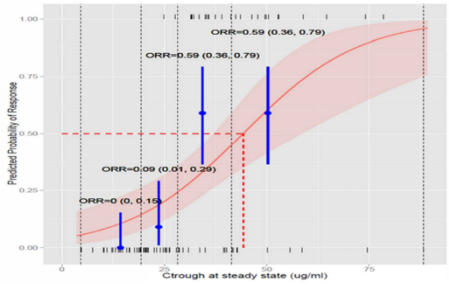
- CL was estimated to be 0.0246 L/h (95% confidence interval (CI): 0.0239, 0.0252) for a typical subject.
- Geometric mean V_{ss} was estimated to be 4.72 L (95% CI: 4.63, 4.82) for a typical subject.
- Geometric mean $t_{1/2}$ was estimated to be 6.1 days (95% CI: 5.8, 6.3) for a typical subject.
- Based on PopPK model, the steady state is expected to be reached by the 3rd dosing cycle and the accumulation ratio is 1.25 which is consistent with the $t_{1/2}$ of 6 days and 2-week dosing interval.
- Body weight was found to affect CL, central volume of distribution (V1) and peripheral volume of distribution (V2), with all 3 parameters increased as body weight increased.
- Male subjects had a 19.9% higher CL and 20.3% higher V1 than female subjects after correction for body weight. The changes in simulated AUC_{SS} between the sexes are not clinically meaningful.
- The model predicted that patients with mMCC had a smaller CL of 22.4%, and a higher exposure than patients with other tumor types.
- There was an influence of baseline tumor size on avelumab CL. Avelumab CL increased with increasing baseline tumor size. This change is considered not clinically meaningful.
- There was an influence of albumin concentrations on avelumab CL. Avelumab CL decreased with increasing albumin concentration. Based on the simulated AUCss values, the change is considered not clinically meaningful.
- The influence of immunogenicity was only significant on V2. No change in the simulated AUC_{ss} values was observed.
- There was no influence of renal or hepatic impairment on CL and thus, no dose adjustment is needed in patients with renal or hepatic impairment.
- PopPK analysis did not find an influence on avelumab CL of any of the concomitant medications included in the analysis. Avelumab is not expected to have an effect on the PK of other drugs.
- Avelumab did not induce cytokines *in vivo* in human subjects to concentrations needed to affect transporters involved in the distribution or CYP450 metabolism for small molecule drugs.

[Serum concentration of several major circulating cytokines including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, interferon-γ (**IFNγ**) and tumor necrosis factor-α (**TNFα**) were measured in Study -001 at serial timepoint up to 85 days after doses of 1, 3, 10, and 20 mg/kg. IFNγ was transiently increased to 2.7±1.9 pg/mL in the 10 mg/kg cohort samples on Day 3 and was down to baseline levels of 1.9±1.6 pg/mL on Day 15. TNFα was transiently increased to 11±10.5 pg/mL in the 10 mg/kg cohort samples on Day 8. Overall, cytokine levels varied in serum with dose and time, but no clear pattern emerged.]

Exposure-Efficacy Analyses: The exposure-efficacy analyses used data from 88 patients with mMCC treated with avelumab in Study -003. Patients were classified as responder or non-responder based on the primary endpoint best overall response (BOR). Logistic regression was used to assess the relationship between BOR and predicted concentrations at the end of the dosing interval at steady state ($C_{trough,ss}$). An apparent $C_{trough,ss}$/BOR

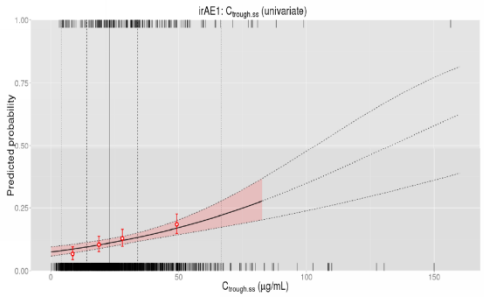
relationship was identified, where a higher exposure was associated with a higher rate of response in mMCC.

Figure 35 Observed ORR and Predicted Probability of Response versus Trough Concentration at the Steady State



Exposure-safety Analyses: The exposure-safety analyses used data from all 1629 subjects treated with avelumab and who had PK data in Studies -001 (N=1490), -002 (N=51) and -003 (N=88). Avelumab exposure was a weak factor associated with an increase in immune-related adverse event (irAE) incidence. The estimated probability of experiencing an irAE increased modestly with increasing avelumab exposure. The estimated probability of experiencing treatment-emergent adverse events (TEAEs) or infusion-related reactions (IRRs) did not increase with increasing avelumab exposure.

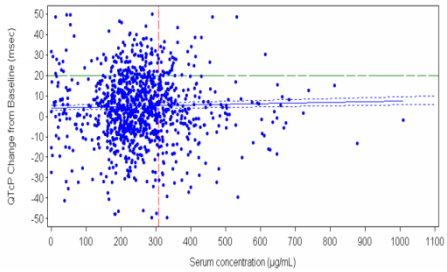
Figure 39 Relationship between Probability of irAE and Ctrough,ss



Exposure-QTc Analysis

A total of 2194 time-matched singlet locally-read 12-lead ECG and avelumab concentrations were collected from a total of 689 study subjects from Studies -001, -002 and -003. Exposure-QTc analysis show that the effect of avelumab on QTc or QTc change from baseline (ΔQTc) is minimal for the QT corrected for heart rate by Fridericia's formula (QTcF) and the QT corrected via a project specific factor (QTcP), indicating that avelumab does not have a clinically meaningful effect on cardiac repolarization.

Figure 42 QTcP Change from Baseline versus Avelumab Concentration, with Diphenhydramine Co-administration



Immunogenicity Assessment: The incidence of immunogenicity is low and ADA against avelumab did not appear to impact PK, safety, and efficacy.

- Treatment-emergent ADA incidence was 49/1383 subjects (3.5%) across the integrated safety analysis population including subjects from Studies -001 and -003. Titers were generally low across ADA-positive subjects, with no clear relationship between the duration of immunogenicity response and the maximum observed titer.
- ADA ever positive subjects had numerically lower C_{trough} than ADA never positive subjects; causality could not be established as C_{trough} within subjects was similar before and after seroconversion.

Concentration at the end of infusion (CEOI) was similar between ADA ever positive subjects and ADA never positive subjects. ADA was only retained in the final PopPK model for V_2, as ADA was not identified as a significant covariate during Pop PK model development for CL and V1. Together, the data suggest an association with C_{trough} and V_2 but not AUC_{ss} and no clinically meaningful impact.

- Infusion-related Reactions (IRRs) were reported in 21.6% and 24.2% of subjects in Studies -003 and -001, respectively.
- A greater percentage of ADA ever positive subjects had IRRs (19/56; 33.9%) versus ADA never positive subjects (344/1428; 24.1%) in the integrated safety analysis population. This appears to be an association rather than causation as only 4 of 56 ADA ever positive subjects had at least 1 IRR at or after ADA seroconversion; 3 of these 4 subjects did discontinue treatment due to IRRs. No significant impact on the safety profile was identified as the numerical increase does not represent a change in the risk assessment nor demonstrate a need to monitor immunogenicity separate from observing IRRs in the clinic.
- The presence of ADA did not preclude initial response to avelumab treatment nor continued response after ADA seroconversion, as 2 of 3 ADA-positive subjects with mMCC responded to avelumab treatment in Study EMR100070-003: 2 partial responses (PR).

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Table 2 Clinical Studies with Clinical Pharmacology Components

Protocol No/Location	Study population (N)	PK/ADA sampling	Treatments
EMR100070-001 (Phase I US (IND 115747), Belgium, Czech Republic, France, Germany, Hungary, Korea, Poland, Taiwan (Republic of China), and UK EudraCT number: 2013-002834-19 (VHP No. 341)	Adult subjects with metastatic or locally advanced solid tumors and expansion to selected indications. (1490 enrolled as of 20 November 2015)	Serial PK sampling during the first dose interval of the dose escalation cohorts (53 subjects) and expansion cohorts (25 subjects) in CRC and CRPC expansion cohorts: prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours, and 24, 36, 48 hours post the first infusion Sparse PK sampling at trough and/or the end of infusion throughout the study on multiple visits in all cohorts including the aforementioned dose escalation, CRC, and CRPC cohorts on visits beyond the first dose interval ADA sampling at baseline, prior to dosing throughout the study and at the End-of-Treatment visit	Avelumab administered via iv infusion once every 2 weeks Dose escalation phase: 1.0 mg/kg (n = 4) 3.0 mg/kg (n =13) 10.0 mg/kg (n =15) 20.0 mg/kg (n =21) Treatment expansion phase: 10.0 mg/kg (n = 1437)
EMR100070-002 (Phase I) Japan	Adult Japanese subjects with metastatic or locally advanced solid tumors, with expansion in subjects with gastric cancer. (51 enrolled as 20 November 2015)[a]	Serial PK sampling during the first dose interval of the dose escalation cohorts (17 subjects): prior to and at the end of the 1-hour infusion, and at 0.5, 1, 2, 4, 6, and 12 hours, and optional 24, 36, 48 hours post the first infusion Sparse PK sampling at trough and/or the end of infusion throughout the study in gastric cancer expansion cohort and on multiple visits beyond first dose interval in the dose escalation cohorts ADA sampling at baseline, prior to dosing throughout the study and at the End-of-Treatment visit	Avelumab administered via iv infusion once every 2 weeks Dose escalation phase: 3.0 mg/kg (n = 5) 10.0 mg/kg (n = 6) 20.0 mg/kg (n = 6) Treatment expansion phase: 10.0 mg/kg (n = 34)
EMR100070-003 (Phase II) US (IND 119394), Australia, Austria, France, Germany, Italy, Japan, Spain, and Switzerland EudraCT number: 2014-000445-79 (VHP No. 531)	Adult subjects who have received at least 1 line of previous chemotherapy for the treatment of mMCC. (88 enrolled and treated with 6 months minimum follow-up time as of Mar 3rd, 2016)	Sparse PK sampling including pre-dose, at the end of infusion and 2 to 8 hours after the end of infusion on multiple visits throughout the study ADA sampling for baseline, prior to dosing throughout the study and at the End-of-Treatment visit	Avelumab administered via iv infusion once every 2 weeks 10 mg/kg (n=88)

ADA: anti-drug antibody; CRC: colorectal cancer; CRPC: castrate-resistant prostate cancer; IND: investigational new drug; iv: intravenous; mMCC: metastatic Merkel cell carcinoma; n: number; PK: pharmacokinetic(s); UK: United Kingdom; US: United States of America; VHP: voluntary harmonization procedure.

a Enrollment numbers see Table 30.

Table 3 **Demographic Data Continuous Variables for all Subjects with Pharmacokinetic Information**

Covariate	EMR100070-001 (n=1490)	EMR100070-002 (n=51)	EMR100070-003 (n=88)	Total (n=1629)
Age (y)	63 {60.4} (20-91) [0]	62 {60.1} (30-77) [0]	72.5 {68.7} (33-88) [0]	63 {60.8} (20-91) [0]
Weight (kg)	70.6 {71.1} (30.4-204) [4]	55.5 {55.3} (35.2-89.3) [0]	82.7 {80.9} (47-153) [1]	70.5 {71} (30.4-204) [5]
Height (cm)	168 {168} (135-195) [25]	163 {161} (138-177) [0]	173 {171} (150-185) [1]	168 {168} (135-195) [26]
BSA (m^2)	1.8 {1.8} (1.2-2.62) [30]	1.6 {1.58} (1.27-2.01) [0]	1.96 {1.93} (1.43-2.47) [2]	1.8 {1.8} (1.2-2.62) [32]
AST (U/L)	22 {23.4} (2-210) [5]	24 {24.1} (12-122) [0]	26 {27.7} (10-113) [0]	23 {23.7} (2-210) [5]
ALT (U/L)	19 {NC} (0-185) [5]	16 {16.4} (6-70) [0]	18.5 {18.3} (5-62) [0]	19 {NC} (0-185) [5]
Total bilirubin (μmol/L)[a]	6.84 {6.9} (0.51-12000) [8]	10.3 {9.13} (3.42-20.5) [0]	6.84 {7.19} (3.3-26) [0]	6.84 {6.98} (0.51-12000) [8]
Albumin (g/L)	39 {38.3} (0.04-430) [5]	37 {39} (21-310) [0]	40.4 {39.8} (24.1-53) [0]	39 {38.4} (0.04-430) [5]
Prothrombin (intl. normalized ratio)	1 {1.08} (0.71-72) [6]	1.03 {1.04} (0.93-1.24) [0]	1.04 {1.08} (0.84-2.94) [0]	1 {1.08} (0.71-72) [6]
Creatinine (μmol/L) [a]	72.5 {74.7} (17.7-2560) [10]	62.8 {66.7} (33.6-114) [0]	81.3 {83} (34.5-194) [0]	73.4 {74.8} (17.7-2560) [10]
Creatinine clearance (mL/min) [a]	83.1 {82.4} (2.2-150) [11]	73 {75.5} (40.8-139) [0]	77 {79.3} (41.7-150) [0]	82.3 {82} (2.2-150) [11]
Total protein (g/L)	70 {68.2} (0.06-689) [8]	64 {64.7} (49-77) [0]	69 {68.9} (53-89) [0]	70 {68.2} (0.06-689) [8]
eGFR (mL/min/1.73 m^2)	86.6 {84.9} (1.3-398) [10]	106 {102} (51.4-178) [10]	75.2 {78.4} (32.6-177) [10]	86.5 {85.0} (1.3-398) [10]

Source: Module 5.3.3.5 PopPk report Table 5.

NC: not calculable. BSA: body surface area; AST: aspartate transaminase; ALT: alanine transaminase; eGFR: estimated glomerular filtration rate.

Numbers are median {geometric mean} (range) [missing (absolute number)].

a Extreme values of covariates were observed in 2 subjects. Extreme values were not able to inappropriately influence covariate selection during Pop PK modeling as values were capped (refer to Module 5.3.3.5 PopPk report Section 5.4.3).

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/s/

SAFAA BURNS
11/10/2016

JEANNE FOURIE ZIRKELBACH
11/10/2016