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Human Medicines Division

# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## Bavencio

avelumab

Procedure no: EMEA/H/C/004338/P46/009

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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| **Description** | **Date** |
| Start of procedure | 27 Dec 2021 |
| CHMP Rapporteur Assessment Report | 31 Jan 2022 |
| CHMP members comments | 14 Feb 2022 |
| Updated CHMP Rapporteur Assessment Report | 17 Feb 2022 |
| CHMP adoption of conclusions: | 24 Feb 2022 |

**Rapporteur: Filip Josephson**

# 1. Introduction

On 29th of November 2021, the MAH submitted a completed paediatric study MS100070-0306 report for Bavencio (avelumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that study MS100070-0306 () is part of a clinical paediatric development program for Bavencio. The initial avelumab PIP was agreed on 17-Mar-17 (P/0071/2017).

Here Study MS100070-0306 is presented as a stand-alone study based on the phase I part. The phase II was removed due to failure of avelumab monotherapy to lead to objective responses for the solid tumours tested in phase I. This discontinuation was part of agreed avelumab PIP modification.

## *2.2. Information on the pharmaceutical formulation used in the study*

Avelumab was administered as an intravenous infusion. Dose was adjusted based on weight.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for study MS100070-0306

### 2.3.2. Clinical study – MS100070-0306

### Description

This was a multicenter, open-label, international, Phase I/II study to evaluate the dose, safety and tolerability, antitumour activity, pharmacokinetic (PK), and pharmacodynamics of avelumab in paediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumours and lymphoma. The study was intended to consist of 2 parts: the dose-finding part (Phase I) and the tumour-specified expansion part (Phase II). The study was finished after dose-finding part (Phase I). Phase II was cancelled due to limited clinical benefit of PD-L1 monotherapy in paediatric patients. This discontinuation was part of agreed avelumab PIP modification.

### Methods

#### *Study participants*

Paediatric subjects aged 0 to < 18 years of age with refractory or relapsed malignant solid tumours (including central nervous system [CNS] tumours) and lymphoma for which no standard therapy is available or for which the subject was not eligible for the existing therapy.

***Treatments***

Avelumab was administered once every 2 weeks (duration of 1 cycle was 14 days) until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.

Subjects received an intravenous infusion of avelumab over 1 hour (− 10 minutes/+ 20 minutes, i.e., 50 to 80 minutes) once every 2 weeks. The subject received either 10 mg/kg or 20 mg/kg of avelumab dose. The dose of avelumab was calculated based on the weight of the subject determined within 72 hours prior to administration. The dose of avelumab used for the previous administration could have been repeated if the change in the subject's weight was within 10% of the weight used for the previous dose calculation.

Premedication with an antihistamine (H1 receptor blocker such as diphenhydramine) and paracetamol for the first 4 doses was mandatory in all subjects treated with avelumab.

Subjects received treatment with avelumab until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred. Subjects who would have experienced complete response (CR) were to be treated for a minimum of 12 months based on clinical judgment of benefit and/or until confirmed progression per immune-related Response Evaluation Criteria in Solid Tumours (irRECIST), unacceptable toxicity, or any criterion for withdrawal occurred, after confirmation of response.

The most commonly used concomitant medications were paracetamol, fentanyl and furosemide.

***Objective(s) & endpoints***

Objectives and endpoints for Phase I part of the study are presented below:

| | Objective | Endpoint |
|---|---|---|
| **Primary Objective** | To evaluate the safety and tolerability of avelumab | Primary Endpoint:<br>Occurrence and severity of treatment-emergent adverse events (TEAEs) ≥ Grade 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03<br>Secondary Endpoints<br>Vital signs (including blood pressure and heart rate)<br>Occurrence and severity of TEAEs, adverse events (AEs) of special interest, and treatment-related AEs, and incidence of laboratory abnormalities as graded by NCI-CTCAE Version 4.03 |
| | To determine the recommended Phase II dose (RP2D) of avelumab in pediatric subjects 0 to < 18 years of age with solid tumors and lymphoma | Primary Endpoint:<br>Dose-limiting toxicities (DLTs) to determine RP2D |
| **Secondary Objective** | To assess antitumor activity of avelumab by determining the Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and as adjudicated by the Investigator in pediatric subjects with solid tumors and lymphoma treated with avelumab | Secondary Endpoint:<br>Confirmed Best Overall Response (BOR) according to RECIST 1.1 and as adjudicated by the Investigator |
| | To assess progression-free survival (PFS) based on Investigator assessments, duration of response (DOR), time to response (TTR), and overall survival (OS) | Secondary Endpoints:<br>DOR, TTR, PFS per RECIST 1.1 and as adjudicated by the Investigator and OS |
| | To characterize the pharmacokinetics (PK) of avelumab | Secondary Endpoint:<br>Single- and multiple-dose PK profiles of avelumab (ie, $C_{max}$, AUC, $t_{1/2}$, and $C_{trough}$, as data permit) |
| | To assess the immunogenicity of avelumab | Secondary Endpoint:<br>Immunogenicity as measured by avelumab anti-drug antibodies (ADA), including neutralizing antibodies (nAbs) |
| | To evaluate programmed death ligand-1 (PD-L1) expression; tumor-infiltrating T-cell activity; T-cell population; and T cell, B-cell and natural killer cell (NK-cell) numbers in tumor tissue at Baseline and at confirmed progression (if tumor tissue is obtained) | Secondary Endpoint:<br>Assessment of tumor PD-L1 expression; tumor-infiltrating T-cell activity; T-cell population; and T-cell, B-cell, and NK-cell numbers at Baseline and at confirmed progression (if tumor tissue is obtained) |
| | To measure changes in vaccination-related antibody concentrations (diphtheria, tetanus, and pneumococcal conjugate) | Secondary Endpoint:<br>Vaccination-related antibody concentrations |

| | Objective | Endpoint |
|---|---|---|
| **Exploratory Objective** | To explore the antitumor effect of avelumab by immune-related RECIST (irRECIST) and as adjudicated by the Investigator (immune-related BOR [irBOR], immune-related PFS [irPFS]) | Exploratory Endpoints:<br>irBOR and irPFS |
| | To explore molecular, cellular, and soluble markers that may be relevant to the mechanism of, or response/resistance to, avelumab | Exploratory Endpoints:<br>Potential predictive and pharmacodynamics biomarkers in peripheral blood and tumor tissues that may include, but are not limited to, inflammatory cytokine levels, blood-based gene expression profile, tumor mutation burden, level of tumor DNA in plasma, and immunocompetent cell composition in the tumor microenvironment |
| | To explore changes in T-cell population, and T-cell, B-cell, and NK-cell numbers in blood samples | Exploratory Endpoints:<br>Changes in T-cell population and T-cell, B-cell, and NK-cell numbers in blood samples. |
| ADA = antidrug antibody; AEs = adverse events; BOR = best overall response; $C_{max}$ = maximum serum concentration observed postdose; $C_{trough}$ = minimum postdose trough serum concentration; DLT = dose-limiting toxicity; DNA = deoxyribonucleic acid; DOR = duration of response; irBOR = immune-related best overall response; irPFS = immune-related progression-free survival; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NAbs = neutralizing antibodies; NK = natural killer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; RP2D = recommended Phase II dose; TEAEs = treatment-emergent adverse events; TTR = time to response. | | |

***Sample size***

Between 12 and 36 subjects were planned to be enrolled in the Phase I part of the study, depending on the required dose-escalation steps according to the Bayesian design.

***Randomisation and blinding (masking)***

Non-randomized study.

***Statistical Methods***

All statistical summaries were descriptive in nature.

Descriptive statistics were used for PK parameters.

## Results

***Participant flow and recruitment***

First subjects first dose was administrated 19 March 2018 and last subject last visit for Phase I was 31 May 2021.

A total of 26 subjects were screened for participation in the Phase I part of the study. A total of 21 subjects were enrolled and received at least 1 dose of study treatment; 6 subjects in the avelumab 10 mg/kg treatment group and 15 subjects in the avelumab 20 mg/kg treatment group. As PK exposure in the first 6 paediatric subjects was lower than expected, compared with the adult exposure, the Safety Monitoring Committee (SMC) agreed that the dose should be escalated to 20 mg/kg for the next cohort of subjects. At the final analysis (data cut-off date 27 July 2021) for the Phase I part of the study, all 21 subjects had discontinued the study treatment.

***Baseline data***

There was a similar number of male and female subjects in the Phase I part of the study (52.4% and 47.6%, respectively). The majority of the subjects were Asian (71.4%) and the subjects' age ranged from 3 to 17 years (median of 12 years). A similar proportion of subjects were in age category of 1 to 12 years (52.4%) and >12 years (47.6%). Overall, the mean Lansky performance status and Karnofsky performance status was 77.5 and 90.0, respectively.

The primary tumour categories were soft tissue/bone sarcoma (12 subjects [57.1%]), CNS (8 subjects [38.1%]), and GI (1 subject [4.8%]). One subject with primary GI tumours was enrolled in the study and was included in the avelumab 10 mg/kg dose group, while all 8 subjects with CNS tumours were included in the avelumab 20 mg/kg dose group.

The median time from initial cancer diagnosis to first avelumab dose was 22.24 months (minimum: 4.3 months; maximum: 168.0 months). For subjects with metastatic disease (14 subjects [66.7%]), there was some variation in the time from metastatic disease to first avelumab dose, with a median time of 10.33 months (minimum: 0.3 months; maximum: 53.5 months).

All subjects (100.0%) had at least 1 prior anticancer surgery and 10 subjects (47.6%) had at least 1 prior radiotherapy. All subjects (100.0%) had received at least 1 prior anticancer drug therapy with 9 subjects (42.9%) having had ≥ 4 prior anticancer drug therapy regimens. All subjects had received cytotoxic therapy, 2 subjects (9.5%) had targeted therapy, 1 subject (4.8%) had monoclonal antibodies therapy, and 1 subject (4.8%) had therapy recorded as "other.

The majority of the subjects in both the treatment groups had negative status for PD-L1 expression (n=11). Among those who tested positive for PD-L1 expression, 5 subjects were positive at the ≥1% cutoff, 4 subjects at the ≥ 5% cutoff, 3 subjects at the ≥ 25% cutoff, 2 subjects at the ≥ 50% cutoff, and 2 subjects at the ≥ 80% cutoff.

***Number analysed***

All 21 subjects (100.0%) who received study treatment were included in the FAS, SAF, PK Analysis Set, Biomarker Analysis Set, and Immunogenicity Analysis Set.

A total of 18 subjects (85.7%) were included in the DLT Analysis Set, defined as subjects who received all study treatment administrations in the DLT evaluation period (first 2 cycles of treatment) or stopped treatment because of DLTs in the DLT evaluation period. One subject was not included in the DLT Analysis Set because the subject received only 1 dose due to an AE. Of the 3 subjects not included in the DLT Analysis Set, 2 subjects were considered not to be DLT evaluable during the study conduct since 2 subjects did not complete the DLT observation period (28-day period [2 cycles] beginning with the first avelumab administration) and 1 subject was considered not to be DLT evaluable because he stopped due to early PD before second study drug administration. All three subjects were replaced in the respective dose cohort in agreement with the SMC.

***Pharmacokinetic results***

A previously validated ligand binding assay was used for the quantification of avelumab. In the bioanalytical study report, it is stated that method is based on method. Validation report. QCs, calibration standards and the incurred sample reproducibility performed within preset criteria in the within study validation. Study samples were analysed within their long-term storage stability.

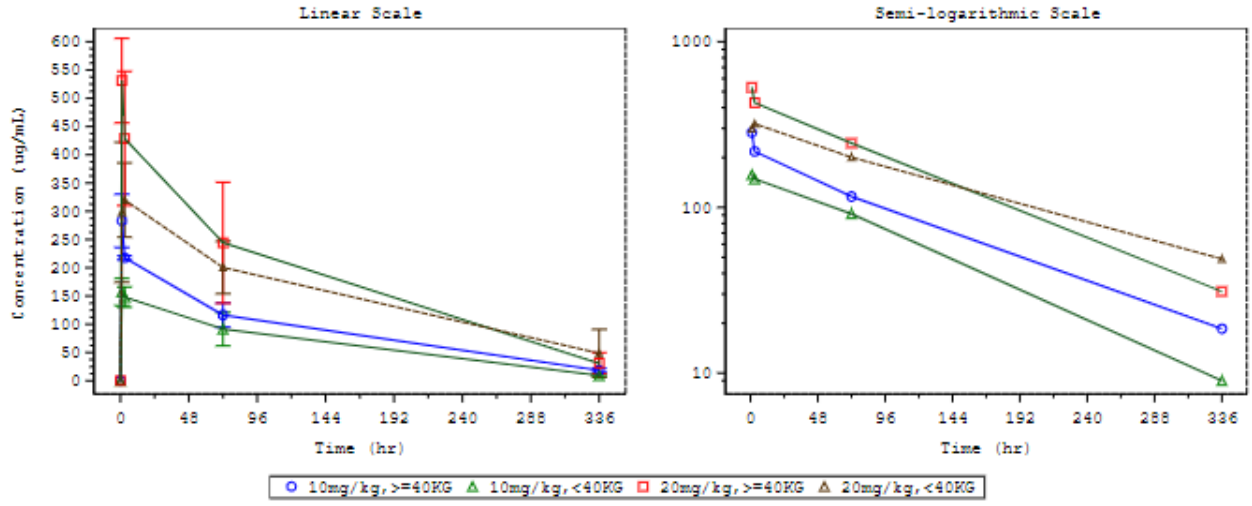
There were no important protocol deviations affecting PK. No subjects were excluded from PK Analysis. Based on safety and preliminary PK exposure data in the 10 mg/kg group, it was recommended by the

SMC to escalate the dose to 20 mg/kg. PK parameters and the corresponding PK profiles are summarised by dose for all patients as well as stratified by bodyweight in Table 1 and Figure 1. Subjects who received 10 mg/kg weighed 18.5 to 65.6 kg and subjects who received 20 mg/kg weighed 13.4 to 78.7 kg. Since only 1 subject in both 10 mg/kg and 20 mg/kg groups was positive for ADA, no conclusions could be made on association between ADA status and PK.

*Table 1: PK parameters of avelumab following the first iv dose*

| Dose group, BW category | Variable (units) | N | Mean | Standard deviation | Median | GeoMean | Geo CV% |
|---|---|---|---|---|---|---|---|
| 10 mg/kg, ALL | $C_{max}$ (µg/mL) | 6 | 200 | 70.5 | 176 | 190 | 34.5 |
| | $AUC_{0-336}$ (µg*h/mL) | 6 | 19,400 | 5,537 | 18,600 | 18,800 | 29.2 |
| | $C_{trough}$ (µg/mL) | 6 | 12.2 | 5.44 | 10.5 | 11.2 | 44.9 |
| | $C_{EOI}$ (µg/mL) | 6 | 199 | 70.86 | 175.0 | 190 | 34.7 |
| 10 mg/kg, < 40 kg | $C_{max}$ (µg/mL) | 4 | 158 | 24.5 | 161 | 157 | 16.2 |
| | $AUC_{0-336}$ (µg*h/mL) | 4 | 16,300 | 3,211 | 15,300 | 16,000 | 19.1 |
| | $C_{trough}$ (µg/mL) | 4 | 8.99 | 2.14 | 8.66 | 8.80 | 23.6 |
| | $C_{EOI}$ (µg/mL) | 4 | 157 | 24.16 | 159 | 156 | 16.0 |
| 10 mg/kg, ≥ 40 kg | $C_{max}$ (µg/mL) | 2 | 283 | 47.2 | 283 | 281 | 16.9 |
| | $AUC_{0-336}$ (µg*h/mL) | 2 | 25,700 | 1,938 | 25,700 | 25,600 | 7.6 |
| | $C_{trough}$ (µg/mL) | 2 | 18.5 | 3.65 | 18.5 | 18.3 | 20.0 |
| | $C_{EOI}$ (µg/mL) | 2 | 283 | 47.2 | 283 | 281 | 17.0 |
| 20 mg/kg, ALL | $C_{max}$ (µg/mL) | 15 | 397 | 110 | 363 | 384 | 27.3 |
| | $AUC_{0-336}$ (µg*h/mL) | 14 | 44,400 | 9,682 | 44,400 | 43,500 | 22.5 |
| | $C_{trough}$ (µg/mL) | 14 | 43.7 | 37.1 | 37.5 | 34.8 | 77.8 |
| | $C_{EOI}$ (µg/mL) | 15 | 370 | 143.9 | 363 | 337 | 52.0 |
| 20 mg/kg, < 40 kg | $C_{max}$ (µg/mL) | 10 | 345 | 74.1 | 359 | 338 | 20.4 |
| | $AUC_{0-336}$ (µg*h/mL) | 10 | 42,200 | 9435 | 39,700 | 41,300 | 21.2 |
| | $C_{trough}$ (µg/mL) | 10 | 48.8 | 42.1 | 37.5 | 39.4 | 70.1 |
| | $C_{EOI}$ (µg/mL) | 10 | 305 | 118.5 | 320 | 279 | 51.4 |
| 20 mg/kg, ≥ 40 kg | $C_{max}$ (µg/mL) | 5 | 503 | 94.2 | 525 | 496 | 19.4 |
| | $AUC_{0-336}$ (µg*h/mL) | 4 | 50,200 | 8849 | 50,900 | 49,600 | 18.3 |
| | $C_{trough}$ (µg/mL) | 4 | 31.1 | 18.5 | 32.6 | 25.5 | 97.5 |
| | $C_{EOI}$ (µg/mL) | 5 | 501 | 93.4 | 525 | 494 | 19.2 |

Source: 15.4.1.2, 15.4.1.4, 15.4.1.5, 15.4.1.21, 15.4.1.22, 15.4.1.19.
BW = body weight; CV% = percent coefficient of variation; $C_{EOI}$ = end of infusion concentration
GeoMean = geometric mean.




SD = standard deviation. Only data with n>=3 were summarized.
As an exception, descriptive stats is also provided when n=2.

*Figure 1: Mean (SD) serum concentration/time profile of avelumab following the first iv dose stratified by bodyweight*

Ctrough and $C_{EOI}$ over time is presented in Table 2 and Table 3, respectively.

*Table 2: Serum trough concentrations of avelumab after iv administration*

| Dose Group | Variable | Day (Week) | n | Mean (ug/mL) | Median (ug/mL) | SD (ug/mL) | GeoMean (ug/mL) | GeoCV% |
|---|---|---|---|---|---|---|---|---|
| 10mg/kg | Ctrough | 15 (W3) | 6 | 12.2 | 10.5 | 5.444 | 11.2 | 44.9 |
| | | 29 (W5) | 6 | 12.1 | 11.4 | 5.263 | 11.3 | 43.9 |
| | | 57 (W9) | 2 | NC | NC | NC | NC | NC |
| | | 85 (W13) | 2 | NC | NC | NC | NC | NC |
| | | 99 (W15) | 2 | NC | NC | NC | NC | NC |
| 20mg/kg | Ctrough | 15 (W3) | 14 | 43.7 | 37.5 | 37.09 | 34.8 | 77.8 |
| | | 29 (W5) | 9 | 64.2 | 44.9 | 40.11 | 55.2 | 61.4 |
| | | 57 (W9) | 8 | 62.0 | 57.8 | 43.04 | 48.4 | 94.6 |
| | | 85 (W13) | 6 | 76.3 | 72.8 | 43.47 | 63.1 | 86.6 |
| | | 99 (W15) | 5 | 63.3 | 52.7 | 40.50 | 54.0 | 70.1 |
| | | 169 (W25) | 3 | 72.3 | 54.7 | 50.74 | 61.4 | 78.9 |
| | | 253 (W37) | 3 | 239 | 117 | 261.5 | 156 | 159.4 |
| | | 337 (W49) | 3 | 67.6 | 57.3 | 25.54 | 64.6 | 36.9 |
| | | 421 (W61) | 2 | NC | NC | NC | NC | NC |
| | | 505 (W73) | 2 | NC | NC | NC | NC | NC |
| | | 589 (W85) | 2 | NC | NC | NC | NC | NC |
| | | 673 (W97) | 2 | NC | NC | NC | NC | NC |
| | | 757 (W109) | 1 | NC | NC | NC | NC | NC |
| | | 841 (W121) | 1 | NC | NC | NC | NC | NC |
| | | 925 (W133) | 1 | NC | NC | NC | NC | NC |

CV% = coefficient of variation expressed as percentage; Geo = geometric; NC = not calculated; SD = standard deviation; Values are listed with a precision of 3 significant figures.

*Table 3: Serum concentrations of avelumab at the end of infusion*

| Dose Group | Variable | Day (Week) | n | Mean (ug/mL) | Median (ug/mL) | SD (ug/mL) | GeoMean (ug/mL) | GeoCV% |
|---|---|---|---|---|---|---|---|---|
| 10 mg/kg | Ceoi | 1 (W1) | 6 | 199 | 175 | 70.86 | 190 | 34.7 |
| | | 29 (W5) | 6 | 162 | 166 | 43.26 | 157 | 29.0 |
| | | 85 (W13) | 2 | NC | NC | NC | NC | NC |
| 20 mg/kg | Ceoi | 1 (W1) | 15 | 370 | 363 | 143.9 | 337 | 52.0 |
| | | 29 (W5) | 9 | 446 | 461 | 91.03 | 437 | 22.8 |
| | | 85 (W13) | 5 | 476 | 483 | 74.17 | 472 | 15.9 |
| | | 169 (W25) | 3 | 433 | 421 | 22.17 | 433 | 5.0 |
| | | 253 (W37) | 3 | 304 | 423 | 211.5 | 222 | 161.3 |

Ceoi = end of infusion concentration; CV% = coefficient of variation expressed as percentage; Geo = geometric; NC = not calculated; SD = standard deviation; Values are listed with a precision of 3 significant figures.

Dose normalised AUC and Cmax, as well as absolute Ctrough are depicted in Figure 2 stratified by bodyweight.

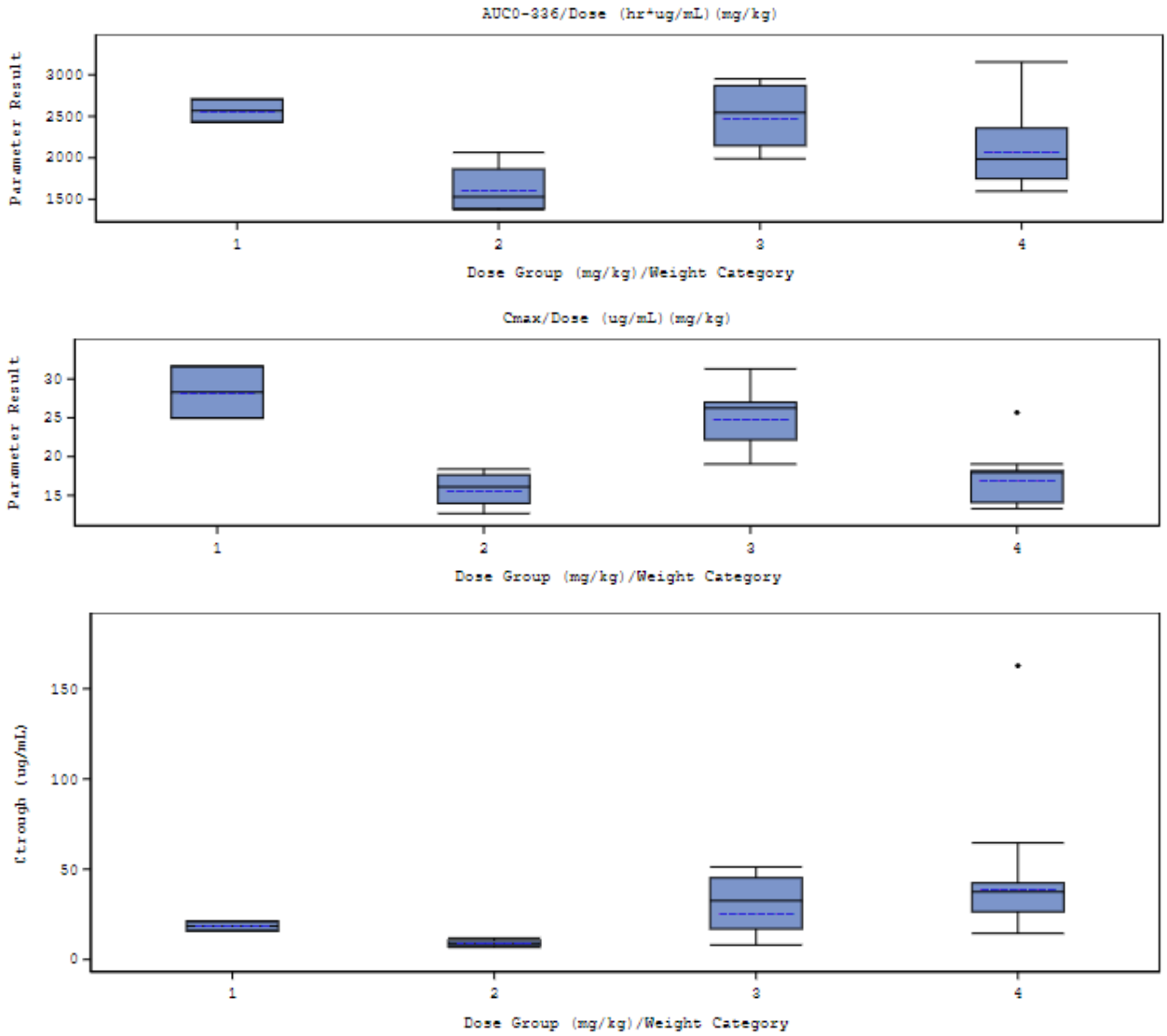



*Figure 2: Box plots of dose-normalised (mg/kg) AUC (top), dose-normalised Cmax (middle) and Ctrough stratified by bodyweight following the first iv dose of avelumab.*

No statistical analysis for PK parameters was performed, but the applicant notes some trends in PK exposures in Cycle 1:

- A trend of lower exposure in paediatric subjects with body weight of < 40 kg compared to those with body weight ≥ 40 kg at the same dose level in both 10 and 20 mg/kg once every 2 weeks dose groups was observed.
- In paediatric subjects with body weight ≥ 40 kg, there was an approximately dose-proportional increase in Cycle 1 median/geometric mean exposures (Cmax, AUC, and Ctrough) from 10 to 20 mg/kg once every 2 weeks. In paediatric subjects with body weight of < 40 kg, there was a trend of a more than dose-proportional increase in median/geometric mean AUC and Ctrough at the same dose level.
- No evidence of association between age and exposure was observed.

- Geometric mean Cycle 1 AUC and Ctrough in the 10 mg/kg dose group with dosing once every 2 weeks appeared lower compared with those in adults at the approved dose (10 mg/kg or 800 mg once every 2 weeks [Novakovic 2020]), especially in subjects with body weight < 40 kg. Median/geometric mean Cycle 1 AUC and Ctrough in the 20 mg/kg dose group were similar or higher compared with those in adults at the approved dose, regardless of body weight.
- The PK profile in the subject who had a DLT at 20 mg/kg was similar to PK profiles in other subjects in the 20 mg/kg once every 2 weeks dose group.
- No consistent trend in change in Ctrough or $C_{EOI}$ over time was observed in the subjects remaining on treatment beyond Cycle 1.

***Efficacy results***

None of the subjects in the avelumab 10 mg/kg or 20 mg/kg dose groups had a CR or PR, therefore the ORR was 0 (95% CI: 0.0, 45.9 and 0.0, 21.8 for each dose level, respectively)

Four subjects (26.7%) in the 20 mg/kg dose group had BOR of stable disease (SD); all had tumours in the CNS category. Three subjects with CNS tumours had sustained SD for at least 6 months. Two subjects experienced a long term stabilization of at least 25 months. All other subjects, regardless of dose level, had BOR of PD or were NE.

***Safety results***

The median duration of therapy was over 8 weeks for subjects in the avelumab 10 mg/kg dose group and nearly 12 weeks for subjects in the avelumab 20 mg/kg dose group. The median number of infusions was 4.0 and 6.0 for avelumab 10 mg/kg and 20 mg/kg dose groups, respectively. The majority of subjects received between 90% and < 110% of the planned dose per cycle. No subjects received ≥ 110% of the planned dose.

One subject (8.3%) in the avelumab 20 mg/kg dose group experienced 3 events (fatigue, hemiparesis, and muscular weakness) that were identified by the SMC as a DLT. The MTD was not reached in paediatric subjects.

At least 1 TEAE was reported in all subjects treated in the study, including 3 subjects (50.0%) in the avelumab 10 mg/kg dose group and 10 subjects (66.7%) in the avelumab 20 mg/kg dose group with at least 1 treatment-related TEAE.

Five subjects (83.3%) in the avelumab 10 mg/kg dose group and 11 subjects (73.3%) in the avelumab 20 mg/kg dose group experienced at least 1 Grade ≥ 3 TEAE; of these, only 1 subject (20 mg/kg dose group) experienced Grade 3 TEAEs considered by the Investigator to be treatment-related

At least 1 serious TEAE was reported in 4 subjects (66.7%) in the avelumab 10 mg/kg dose group and 12 subjects (80.0%) in the avelumab 20 mg/kg dose group, including 2 subjects (13.3%) in the avelumab 20 mg/kg dose group with at least 1 serious treatment-related TEAE.

Treatment-emergent AEs that led to death were reported for 1 subject (16.7%) in the avelumab 10 mg/kg dose group and 3 subjects (20.0%) in the avelumab 20 mg/kg dose group. All TEAEs that led to death had PT as disease progression and none was considered related to treatment.

None of the subjects in the avelumab 10 mg/kg dose group and 8 subjects (53.3%) in the avelumab 20 mg/kg dose group permanently discontinued treatment due to TEAEs; of these 5 TEAEs were reported as disease progression and 3 TEAEs as thrombocytopenia, malignant pleural effusion, and intracranial

hypertension, which were related to disease progression. None of the subjects discontinued avelumab due to a treatment-related TEAE.

At the final analysis for Phase I part of the study, 4 subjects (66.7%) in the avelumab 10 mg/kg dose group and 12 subjects (80.0%) in the avelumab 20 mg/kg dose group had at least 1 serious TEAE. Disease progression and pyrexia were the most commonly reported serious TEAEs in avelumab 20 mg/kg dose group. In the avelumab 10 mg/kg dose group, seriousTEAEs reported were in the form of single case reports only.

There were no treatment-emergent irAEs of Grade ≥ 3, serious irAEs, irAEs leading to permanentstudy treatment discontinuation, or irAEs leading to death. One subject experienced an irAE. The subject, a 6 year-old female with a CNS primary tumour (atypical teratoid rhabdoid tumour), experienced an irAE of Grade 2 hypothyroidism that started on Study Day 42, and was considered related to study treatment. No stop date is recorded for the irAE.The subject received 6 infusions of avelumab 20 mg/kg prior to discontinuing study treatment due to PD on Day 84.

There were no treatment-emergent IRRs of Grade ≥ 3, serious IRRs, IRRs leading to permanent study treatment discontinuation, or IRRs leading to death. In avelumab 10 mg/kg group,1 subject had IRRs after Infusion 1 and Infusion 3, and 1 subject after Infusion 4 or later. In the avelumab 20 mg/kg dose group, 5 subjects had a first onset after the first Infusion, 1 subject after Infusion 2, 1 subject after Infusion 16 and Infusion 17. Infusion-related reactions were: chills, pyrexia, infusion-related reaction, urticaria, and hypotension.

*Immunogenicity*

Blood samples for antidrug antibodies (ADA) assessments (including neutralizing antibodies [nAbs]) were collected predose (within 2 hours prior to study treatment) as specified in the Schedule of Assessments. If the sample was positive for ADA, it was re-analyzed and tested for neutralizing capacity.

A previously validated homogeneous bridging assay was used.. For the analysis of study samples, a cutpoint determined in solid tumour patients was used Similarly, study report  for nAb used the previously validated method, which had increased drug tolerance compared to earlier methods. Twelve (12) individual paediatric human serum lots were analysed to determine whether the adult cutpoint was appropriate. All neat individuals screened negative (100%). All individuals spiked at the LPC () and the HPC () screened positive (100%). Therefore, it is concluded that the cutpoint determined curing validation (0.919) is sufficient.

In the avelumab 10 mg/kg group, only 1 subject (16.7%) had treatment emergent persistent positive ADA results with a titer of. None out of the 15 (0.0%) of the 20 mg/kg subjects were positive for ADA.

In the avelumab 10 mg/kg group, only 1 subject (16.7%) had treatment emergent persistent positive nAb result. None of the 15 (0.0%) of the 20 mg/kg subjects were positive for nAb.

Of the 21 subjects treated in the study, 1 subject in the 10 mg/kg group had treatment-emergent persistent positive ADA and treatment emergent persistent positive nAb result.

## MAH's overall conclusion

Exposures with 20 mg/kg dosing once every 2 weeks were similar or higher compared to those in adults at the approved dose (10 mg/kg or 800 mg once every 2 weeks). In contrast, exposures with 10 mg/kg dosing once every 2 weeks in children in lower body weight category were lower compared to those at the approved dose in adults.

While the MTD in paediatric subjects was not reached and both the 10 mg/kg and 20 mg/kg dose levels were well tolerated, further clinical studies with avelumab monotherapy (including Phase II) are not recommended due to the lack of clinical activity observed in different tumour types. Therefore, an RP2D for monotherapy studies was not determined.

## 2.3.3. Discussion on clinical aspects

In study MS100070-0306 avelumab monotherapy was investigated in paediatric subjects aged 0 to < 18 years of age with refractory or relapsed malignant solid tumours (including central nervous system [CNS] tumours) and lymphoma for which no standard therapy is available or for which the subject was not eligible for the existing therapy.

In total, 21 patients with soft tissue/bone sarcoma (12 subjects [57.1%]), CNS (8 subjects [38.1%]), and GI (1 subject [4.8%]) was included in phase I. Patients received either 10 mg/kg or 20 mg/kg of avelumab every 2 weeks.

Analytical methods for avelumab, ADAs and nAb were previously deemed acceptable however more information about QPS Validation report is needed.

As noted in the EPAR of the initial MAA, in adult patients, the mean avelumab concentration was 252 µg/mL (range 107 to 1108 µg/mL) at the end of infusion and 23.8 µg/ml (range 1.58 to 245 µg/mL) at trough after the first dose. In adult patients given 10 mg/kg, the mean PK parameters after the first dose were the following: Cmax 310 µg/mL, Ctrough 24 µg/mL, $AUC_{0\text{-}336h}$ 25900 hr*µg/mL.

Very few patients are included, therefore data should be interpreted with caution. The applicant´s view that exposure after the first administration was lower in paediatric patients given 10 mg/kg than the reference exposure in adults is agreed, however paediatric patients given 20 mg/kg had a consistently higher exposure than the adult reference interval. The higher exposure did not translate to efficacy in paediatric patients.

Immunogenicity was in line with available data from adult patients.

No objective responses were recorded in the phase I part of the study. Hence, the phase II part of the study was not started.

The safety results presented are limited due to the low number of included patients precluding any firm conclusions. The MTD was not reached and only 1 DLT was recorded. However, the overall safety profile appears to be as expected from the known safety profile of avelumab. No new safety concern was identified.

Currently, the Bavencio SmPC states the following regarding paediatric use:

Section 4.2:

*Paediatric population*

The safety and efficacy of Bavencio in children and adolescents below 18 years of age have not been established.

According to Articles 16 and 17 of Regulation (EC) No 726/2004, results from paediatric studies, even when there is lack of activity, should be included in the SmPC to provide guidance for the prescribers. Therefore, unless otherwise justified, the SmPC section 5.1, and other applicable sections, should be updated with a brief description of the results of study MS100070-0306.

# 3. Overall conclusion and recommendation

☒ **Fulfilled:**

In view of the available data regarding avelumab in paediatric patients with refractory or relapsed solid tumours and lymphoma the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

- Section 4.2 should be amended with a reference to section 5.1
- Section 5.1 of the SmPC should be updated with a brief description of the results of MS100070-0306 (number of patients, the diagnoses and that no responses were seen)
- Section 5.2 of the SmPC should be updated with the doses and exposures reached in paediatric patients, as compared to adult patients.
- Validation report 218-1823 for avelumab should be provided.

# Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

## Non clinical studies

Product Name: Bavencio Active substance: avelumab

| Study title | Study number | Date of completion | Date of submission of final study report |
|---|---|---|---|
| Anti-tumor activity of avelumab in combination with cyclophosphamide in the MC38 tumor model (PIP Study 1) | IONC29062017CX Avelumab CPA | 12 July 2017 | 03 November 2017 (with compliance check EMEA-C1-001849-PIP02-15-M01) |
| Childhood cancer genomic analysis to understand suitability for avelumab (anti-PDL1) treatment (PIP Study 2) | 18-BI0003-0 | 12 February 2018 | 20 December 2018 (with compliance check EMEA-C2-001849-PIP02-15-M02) |
| Non-clinical biomarker study in pediatric tumor tissues (PIP Study 3) | EMR100070-0306 | 14 December 2018 | 20 December 2018 (with compliance check EMEA-C2-001849-PIP02-15-M02) |

## Clinical studies

Product Name: Bavencio Active substance: avelumab

| Study title | Study number | Date of completion | Date of submission of final study report |
|---|---|---|---|
| Population Pharmacokinetic evaluation of clinical trials EMR100070-001, EMR100070-002 and EMR100070-003 and simulations of exposure in pediatric population after a single dose of avelumab (PIP Study 6) | EMR100070-001, EMR100070-002, EMR100070-003 | 29 March 2017 | 03 November 2017 (with compliance check EMEA-C1-001849-PIP02-15-M01) |
| Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma (PIP Study 4) | MS100070-0306 | 31 May 2021 | November 2021 with this Article 46 submission |
| Single-arm, multicenter Phase I/Ib study of avelumab + lenvatinib in children with primary CNS tumors (PIP Study 7) | MS100070_0087 | ongoing | not applicable |
| Randomized, active-controlled study to evaluate efficacy and safety of avelumab in combination with lenvatinib in children from 2 years to less than 18 years of age with a paediatric tumour of the central nervous system selected on the basis of the results of Study 1, Study 2, Study 3, Study 4 and Study 7. (PIP Study 5) | not yet assigned | planned | not applicable |