

Simulation-based assessment of flat dose regimen of an anti-PD-L1 antibody: case study of avelumab

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BACKGROUND

- Avelumab is a human anti-PD-L1 immunoglobulin G1 antibody that has demonstrated meaningful efficacy and clinical activity across various tumor types with a manageable safety profile^{1,2}
- Avelumab 10 mg/kg intravenously Q2W is approved in the USA, European Union, Canada, Australia, Israel, and Switzerland for the treatment of metastatic Merkel cell carcinoma (mMCC); in Japan for curatively unresectable MCC; in the USA and Israel for advanced or metastatic urothelial carcinoma (UC)³ and is in clinical development for other cancer types
- Two population PK models were previously developed based on data obtained after weight-based (doses of 1, 3, 10, or 20 mg/kg Q2W) single-⁴ (PK CYCLE) and multiple-dose (PK SS) infusions⁵ of avelumab. The PK SS model includes a time-varying clearance component similar to models reported for other anti-PD-L1/PD-1 drugs⁵
- Body weight was found to be a significant covariate for clearance and central volume of distribution
- The estimated magnitude of weight exponents on clearance were 0.335 (95% CI: 0.277-0.393) for the PK CYCLE model⁴ and 0.324 (95% CI: 0.260-0.388) for the PK SS model⁵
- In the case of monoclonal antibodies, a flat dose regimen (independent of body weight) is likely to minimize drug waste, facilitate preparation and administration, and reduce pharmacy errors in comparison with weight-based dosing
- In addition, a flat dosing regimen is expected to result in more consistent exposure across patient populations, when the power exponent describing the effect of body weight on clearance, using population PK models, is estimated to be <0.5⁶
- The choice of the flat dose to be considered (800 mg) was based on median body weights of the patients with advanced or metastatic UC and mMCC treated with avelumab (75.6 and 82.3 kg, respectively) and the general population of patients with cancer (close to 80 kg)^{7,8}

OBJECTIVE

- To compare avelumab exposure between weight-based (10 mg/kg every 2 weeks [Q2W]) and flat (800 mg Q2W) dosing regimens using simulations based on 2 previously developed population pharmacokinetics (PK) models describing avelumab PK after single- and multiple-dose infusions

METHODS

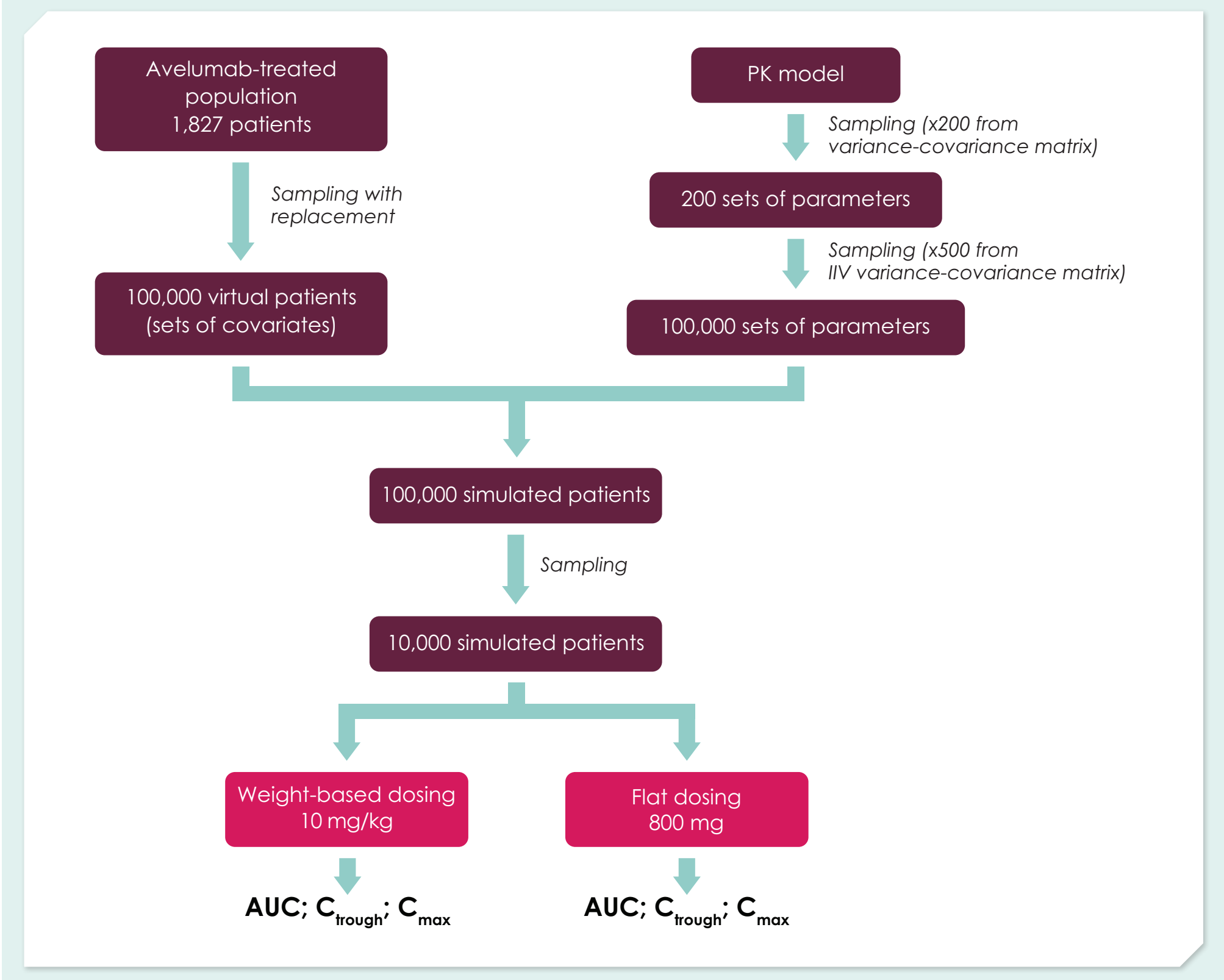
Data

- PK models used in simulations are based on PK data collected from 1,827 patients across 3 clinical trials (JAVELIN Solid Tumor [NCT01772004], JAVELIN Solid Tumor JPN [NCT01943461], JAVELIN Merkel 200 part A [NCT02155647]) for which the median weight was 70.6 kg (range, 30.4-204 kg)

Clinical trial simulations

- The methodology for simulations, outlined in **Figure 1**, is similar using the PK CYCLE and the PK SS models

Figure 1. Clinical trial simulations procedure



- For the PK CYCLE model, a closed-form solution for a linear 2-compartment model was used to calculate the following metrics
 - The area under the curve (AUC_{0-τ}), calculated using the linear trapezoidal rule (τ=336 hours)
 - C_{trough}, defined as the minimum concentration over the dosing interval (τ=336 hours), assumed to occur 335.5 hours after the start of infusion
 - C_{max}, defined as the maximum concentration over the dosing interval (τ=336 hours), assumed to occur at 1 hour after the start of infusion

- For the PK SS model, a “skeleton” data set was constructed to reflect biweekly dosing for 28 weeks (assuming that the steady state had been reached) using the weight-based (10 mg/kg Q2W) and flat (800 mg Q2W) dosing regimens and was simulated using NONMEM. The same metrics used for the PK CYCLE were calculated from the resulting simulated data sets of both models at an assumed steady state between weeks 26 and 28 (τ=336 hours)
- These metrics were used to compare dose regimens in terms of exposure, by quartiles of weight, with the following limits according to the distribution of the overall population (n=1,827):
 - 30.4 to ≤60 kg
 - >60 to ≤70.6 kg
 - >70.6 to ≤84.6 kg
 - >84.6 to ≤204 kg
- In addition, simulation results were compared with observed results after administration of 20 mg/kg to 27 patients in trials EMR100070-001 (n=21) and EMR100070-002 (n=6). In both of these trials, the maximum tolerated dose was not reached at 20 mg/kg
- To assess the variability of derived PK metrics for the 2 dosing regimens, coefficients of variation (CVs) were calculated as the ratio of SD to the mean and summarized per PK metric and per dosing regimen

RESULTS

- Simulations of exposure comparing the weight-based (10 mg/kg Q2W) and flat (800 mg Q2W) dosing regimens after the first cycle (PK CYCLE) and at steady state (PK SS) suggested that the overall variability in exposure was lower with the flat dose (CV) = 27.1% vs 29.0% for AUC_{0-336h}; 38.6% vs 41.2% for AUC_{ss} (**Table 1**)
- The flat 800-mg dose resulted in slightly higher exposures for the simulated population, with the median increasing by approximately 12% and 11% for AUC_{0-336h} and AUC_{ss}, respectively, as would be expected because the median weight of the sampled patients was 70.6 kg (**Table 1**; **Figure 2 and 3**)
- For the weight-based (10 mg/kg) dosing regimen, the highest weight quartile was associated with the highest exposure. The opposite was true for the flat 800-mg dose, ie, the lowest weight quartile was associated with the highest exposure; however, the exposure remained lower than the median exposure observed following administration of 20 mg/kg of avelumab Q2W

Table 1. Median exposure (AUC_{0-336h} and AUC_{ss}) (%CV) by weight quartile based on the PK CYCLE and PK SS models, respectively

Weight group	Median AUC _{0-336h} (mg·h/L) (%CV)		Median AUC _{ss} (mg·h/L) (%CV)	
	10 mg/kg Q2W	800 mg Q2W	10 mg/kg Q2W	800 mg Q2W
>30.4 to ≤60.0 kg	18,408.2 (25.7)	28,213.1 (25.2)	21,340.4 (38.4)	32,751.7 (38.1)
>60.0 to ≤70.6 kg	21,144.8 (25.6)	25,818.8 (25.7)	25,480.5 (37.4)	31,167.4 (37.4)
>70.6 to ≤84.6 kg	22,881.9 (24.9)	23,717.0 (24.6)	28,004.9 (38.4)	29,081.4 (37.9)
>84.6 to ≤204 kg	26,252.4 (25.7)	21,595.3 (25.0)	32,672.0 (37.4)	26,642.0 (37.4)
Overall	21,985.7 (29.0)	24,636.9 (27.1)	26,524.5 (41.2)	29,813.4 (38.6)

Figure 2. Box and whisker plots for the simulated AUC_{0-336h} values for the weight-based (10 and 20 mg/kg Q2W) and flat (800 mg Q2W) dosing regimens for the entire population (left) and split by quartiles of weight (right) using the PK CYCLE model

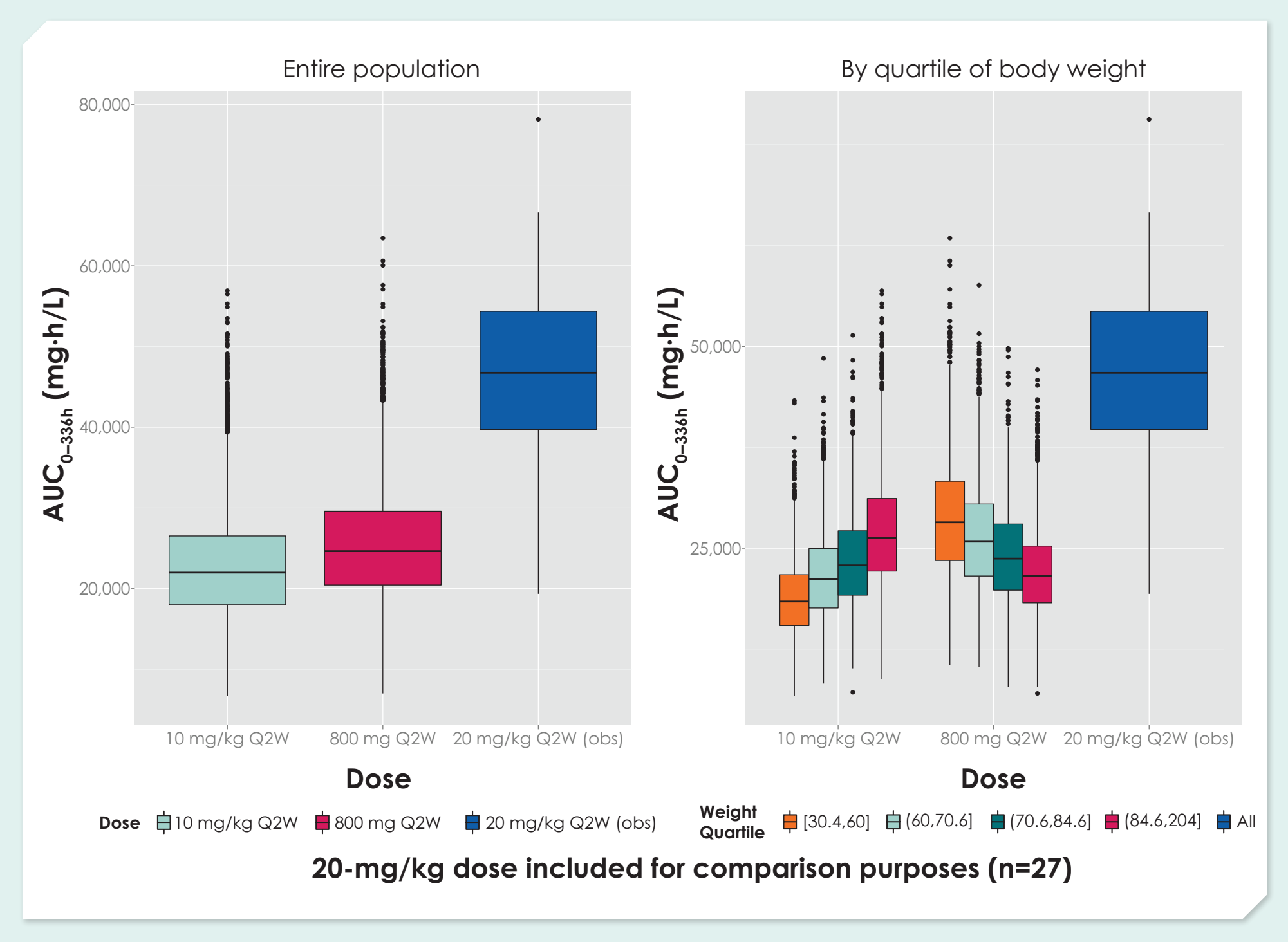
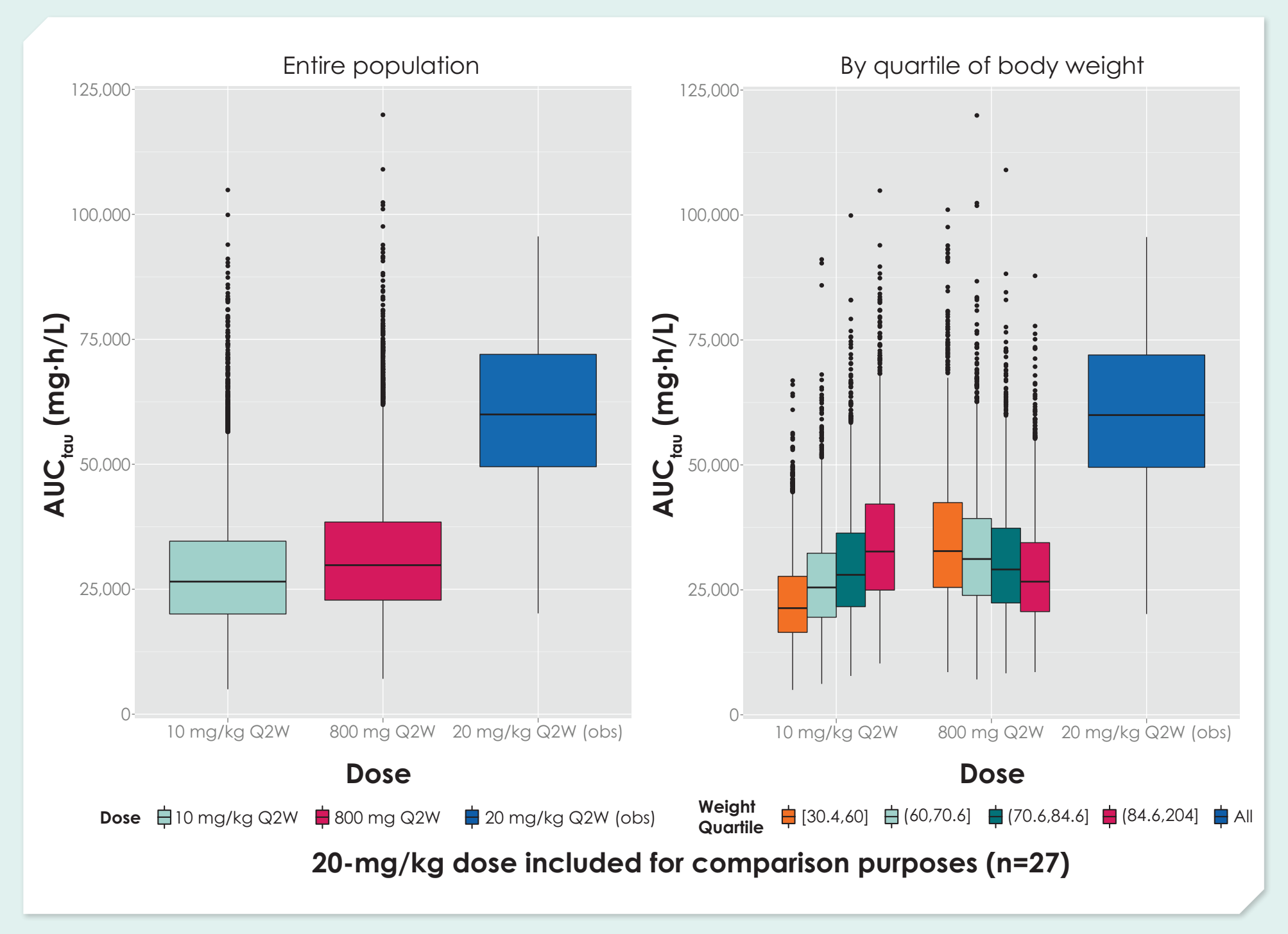


Figure 3. Box and whisker plots for the simulated AUC_{ss} values for the weight-based (10 and 20 mg/kg Q2W) and flat (800 mg Q2W) dosing regimens for the entire population (left) and split by quartiles of weight (right) using the PK CYCLE model



- Simulations based on other exposure metrics confirm the results presented here with AUC, C_{max}, C_{max,ss}, C_{trough}, and C_{trough,ss} predicted with the 800-mg dose were approximately 11%, 11%, 10%, and 12% higher, respectively, compared with the 10 mg/kg dose
- The lowest quartile with the flat dose was associated with the highest exposure but was still below the exposures tested at 20 mg/kg in the dose-finding trial and was comparable to the upper-quartile exposures observed with weight-based dosing. Overall, the simulated exposure for the 800-mg flat dosing regimen fell within the exposure range of avelumab known to be clinically effective and safe

CONCLUSIONS

- Modeling and simulation-based analyses were performed to explore PK exposure for the currently approved weight-based (10 mg/kg Q2W) and the proposed flat (800 mg Q2W) dosing regimens**
- Predicted PK avelumab exposures were similar**
- Lower variability was observed with flat dosing than with weight-based dosing, as expected for monoclonal antibodies with a weight exponent on clearance estimated to be <0.5, in accordance with findings from Wang et al⁶**
- Given the results of these simulations, 800-mg flat dose of avelumab should result in similar exposures and thus maintain the positive benefit risk profile of avelumab while simplifying administration**
- The current simulation was performed to avoid conducting a clinical trial to compare the weight-based and flat dosing regimens**
- A flat dose regimen is currently being evaluated in several trials**

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ACKNOWLEDGMENTS

The authors would like to thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers and at Merck KGaA, Darmstadt, Germany, and EMD Serono, Billerica, MA, USA (a US subsidiary of Merck KGaA, Darmstadt, Germany). The trials reported in this analysis were sponsored by Merck KGaA, Darmstadt, Germany, and are part of an alliance between Merck KGaA and Pfizer Inc, New York, NY, USA. Medical writing support was provided by ClinicalThinking Inc, Hamilton, NJ, USA and funded by Merck KGaA, Darmstadt, Germany, and Pfizer Inc, New York, NY, USA.

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