Population Pharmacokinetics and Exposure-Response Modeling of Daratumumab Subcutaneous Administration in Patients With Light-chain Amyloidosis

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ABSTRACT

The purpose of this study is to characterize the population pharmacokinetics (PopPK) of subcutaneous (SC) daratumumab in combination with bortezomib, cyclophosphamide, and dexamethasone and explore the relationship between daratumumab systemic exposure and selected efficacy and safety endpoints in patients with newly diagnosed systemic light-chain (AL) amyloidosis. The PopPK analysis included pharmacokinetic and immunogenicity data from patients receiving daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone in the ANDROMEDA study (AMY3001; safety run-in, *n*=28; randomized phase, *n*=183). Non-linear mixed-effects modeling was used to characterize the PopPK and quantify the impact of potential covariates. The exposure-response (E-R) analysis included data from all patients in the randomized phase of ANDROMEDA (*n*=388). Logistic regression and survival analysis were used to evaluate the relationships between daratumumab systemic exposure and efficacy endpoints. The E-R analysis on safety was conducted using quartile comparison and logistic regression analysis. The observed concentration-time data of daratumumab SC were well described by a 1-compartment PopPK model with first-order absorption and parallel linear and nonlinear Michaelis-Menten elimination pathways. None of the investigated covariates were determined to be clinically meaningful. Daratumumab systemic exposure was generally similar across subgroups that achieved different levels of hematologic response, and there was no apparent relationship between daratumumab systemic exposure and the investigated safety endpoints. In conclusion, the PopPK and E-R analyses supported the selected 1,800 mg flat dose of daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone regimen for the treatment of light-chain amyloidosis. No dose adjustment was recommended for investigated covariates.

INTRODUCTION

Light-chain amyloidosis is a rare disorder with extracellular deposition of insoluble fibrils in tissues and organs.[1] These fibrils are derived from $CD38^+$ clonal plasma cells that secrete light chains and misfold into insoluble amyloid. Deposition of amyloid in vital organs results in serious and life-threatening organ dysfunction.[1] Amyloid regression is a balance of formation and breakdown; even small amounts of persistent amyloidogenic precursor can continue proteotoxicity as well as the process of amyloid formation. Therefore, achieving less than a complete response (CR) or a very good partial response in light-chain amyloidosis is suboptimal, as a sufficient reduction of light chains with CR is required to reduce both the acute proteotoxicity of the amyloid as well as the continuous organ damage due to amyloid deposits. Traditionally, the general treatment approach involved the use of multiple myeloma treatment regimens to achieve rapid, deep, and durable hematologic responses, as both light-chain amyloidosis and multiple myeloma are clonal plasma cell disorders.[2] However, these treatment regimens, in general, demonstrated similar or lower hematologic responses in light-chain amyloidosis and were associated with higher rates of toxicity. High-dose melphalan followed by autologous peripheral blood stem cell transplantation is one of the commonly used regimens, yet it is associated with substantially higher treatment-related mortality for patients with light-chain amyloidosis (15% to 40%) than for those with multiple myeloma (<5%).[3] High-dose dexamethasone in combination with vincristine and doxorubicin have shown improved outcomes and is well tolerated in patients with multiple myeloma, however, dexamethasone used with the same schedule as in multiple myeloma led to higher toxicity in patients with light-chain amyloidosis. Nearly half of the patients in one study required dexamethasone dose reductions due to dose-limiting toxicities, and treatment-related mortality occurred in 6/86 (7%) of patients.[4] Another study also reported using a milder dexamethasone dose due to higher toxicity rates in

patients with light-chain amyloidosis.[5] In addition, thalidomide is poorly tolerated in patients with light-chain amyloidosis, with adverse events such as bradycardia, hypotension, worsening of serum creatinine, and grade 3 rash, that led to 25% thalidomide discontinuation in one study.[6] In another study, patients experienced adverse events such as progressive edema, cognitive difficulties, dyspnea, and rash; all 12 patients discontinued and the study concluded that patients with light-chain amyloidosis do not tolerate high-dose thalidomide.[7] Taken together, there has been an urgent need for additional treatment options that are efficacious and tolerable for patients with light-chain amyloidosis. Specifically, monoclonal antibodies that target CD38, a cell-surface protein expressed on plasma cells in light-chain amyloidosis, could have high therapeutic potential.[8, 9]

Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor[10-13] and immunomodulatory[14-16] mechanism of action. The results from pivotal clinical trials[17-23] in multiple myeloma led to the approval of intravenous (IV) daratumumab 16 mg/kg as monotherapy and in combination with standard-of-care therapies for multiple myeloma in >80 countries worldwide.[24] Daratumumab IV has shown to be well tolerated with manageable side effects. The most common adverse events are infusion-related reactions, and the median infusion duration is 7 hours for the first infusion and 3 to 4 hours for subsequent infusions.[24] To reduce patient and clinician burden, a subcutaneous (SC) formulation of daratumumab co-formulated with recombinant human hyaluronidase PH20 (rHuPH20; ENHANZE® drug delivery technology, Halozyme, Inc.), given as an 1,800 mg flat dose, was developed and approved.[25] This 1,800 mg SC dose was selected based on a previous phase 1b trial and was further confirmed in a phase 3 open label trial (COLUMBA) in patients with relapsed or refractory multiple myeloma and an exposure-response (E-R) PopPK analysis.[26, 27] Results showed the daratumumab SC 1,800 mg flat dose regimen consistently

produced (1) lower peak-to-trough fluctuations, (2) similar or slightly higher trough levels over time, and (3) lower peak concentrations compared with the approved IV 16 mg/kg dose regimen. These suggest sufficient concentrations have been attained by daratumumab SC 1,800 mg dose regimen. The daratumumab 1,800 mg SC dose also induced deep, durable responses in patients with heavily pretreated multiple myeloma and non-inferiority to 16 mg/kg IV dose in both efficacy and PK were reported in COLUMBA.[28] In addition, the daratumumab SC formulation, administered over 3 to 5 minutes, reduced the rate of infusion-related reactions and improved patient satisfaction and adherence.[25] Furthermore, the SC formulation avoided potential volume burden as seen with the IV formulation in light-chain amyloidosis patients with cardiac and renal involvement, who are at risk for complications related to volume overload. Recently, the Food and Drug Administration (FDA) granted accelerated approval of daratumumab SC in combination with bortezomib, cyclophosphamide, and dexamethasone for light-chain amyloidosis.[29] Approvals have also been granted by other countries in North America, South America, and Europe.

Previously, population pharmacokinetics (PopPK) analyses were performed in patients with multiple myeloma receiving daratumumab IV or daratumumab SC as monotherapy or in combination therapies.[30,27,31] The resulting structural model was a 2-compartment PopPK model with first-order absorption and with parallel linear and nonlinear Michaelis-Menten elimination pathways. Daratumumab SC and daratumumab IV showed similar PopPK model structures except for the absorption phase of SC formulation, which was modeled with a first-order absorption process. A similar E-R relationship for both efficacy and safety endpoints was observed between daratumumab IV and daratumumab SC given as monotherapy or in combination therapy.[27] These results supported

the use of daratumumab SC 1,800 mg flat dose in patients with multiple myeloma, and no dose adjustments were recommended.

We present results from a PopPK and E-R analysis of daratumumab SC in patients with light-chain amyloidosis based on data from the ANDROMEDA study. The key objectives of this analysis were to characterize the PopPK of daratumumab SC and to assess the relationship of daratumumab systemic exposure with selected clinical efficacy and safety endpoints in patients with newly diagnosed light-chain amyloidosis.

METHODS

The ANDROMEDA study protocol and amendments were reviewed by an Institutional Review Board and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients or their legally acceptable representatives provided their written consent to participate in the study.

Clinical study design and patient population

The PopPK and E-R analyses included data from an ongoing, randomized, open-label, active-controlled, multicenter, phase 3 ANDROMEDA study (NCT03201965). The primary efficacy endpoint was the overall hematologic CR rate as defined by consensus recommendations for light-chain

amyloidosis treatment response criteria.[32] A total of 388 patients with light-chain amyloidosis were randomized to receive bortezomib, cyclophosphamide, and dexamethasone with or without daratumumab SC. Patients randomized to the daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone arm received 15 mL daratumumab SC 1,800 mg co-formulated with recombinant human hyaluronidase PH20, weekly in Cycles (C) 1 and 2, every 2 weeks in C3 through C6, and every 4 weeks thereafter until disease progression, start of subsequent therapy, or a maximum of 24 cycles from the start of the study, whichever occurred first. All treatment cycles were 4 weeks (28 days with a ±5 day window) in length. As daratumumab had not been co-administered with bortezomib, cyclophosphamide, and dexamethasone before the initiation of this study, a safety run-in phase was conducted prior to the start of the randomized phase of the study. The daratumumab SC PK and immunogenicity analyses were conducted in samples collected from a total of 211 patients: safety run-in phase (*n* = 28); patients who received daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone in the randomized phase (*n* = 183).

Patient serum samples were collected in the safety run-in phase and in the daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone randomized treatment arm at C1 Day (D) 1 (C1D1) pre-dose; on C1D4 (±1 day); at pre-doses of C1D8, C2D1, and C3D1; on C3D4 (±1 day); at pre-doses of C7D1 and C12D1; at end of treatment (±3 days); and 8 weeks after the last dose of daratumumab SC (±1 week). Pre-dose samples included those collected before (up to 6 hours but not after the start of injection) daratumumab SC administration.

Bioanalytical methods

Serum daratumumab concentration assessment

Daratumumab concentration in human serum samples was determined by a validated electrochemiluminescent immunoassay (ECLIA) method on the Meso Scale Discovery (MSD®) platform. The lowest quantifiable concentration in a sample was 0.2 µg/mL at a 1:40 dilution. At acceptable accuracy and precision, the upper limit of quantification was 3.645 µg/mL and the lower limit of quantification (LLOQ) was 0.005 µg/mL, with an interassay coefficient of variation (CV%) of 8.54% and 6.47%, respectively. The ECLIA method was validated according to the European Medicines Agency, the US FDA, bioanalytical method validation guidances, and industry white papers (EMEA/CHMP/EWP 2011, Guidance for Industry 2018).[33, 34]

Antidrug antibody (ADA) assessment

A validated ADA electrochemiluminescence drug-tolerant ECLIA method (on the MSD® platform) was used originally to determine the presence or absence of anti-daratumumab antibodies (immunogenicity). Daratumumab ADA samples were also assessed with a method that uses polyethylene glycol precipitation and acid dissociation to overcome drug interference and provide enhanced drug tolerance compared to the original ADA method.

Human serum samples containing daratumumab ADA were analyzed by a validated cell-based binding assay based on PerkinElmer's dissociation-enhanced lanthanide fluorescence immunoassay (DELFIA®) technology platform (Waltham, MA, USA) for the ability to neutralize the bioactivity of daratumumab. Anti-rHuPH20 antibodies in human ethylenediaminetetraacetic acid (EDTA) plasma

samples were assessed by a validated and sensitive ECLIA method on the MSD® platform. Human plasma samples confirmed positive for anti-rHuPH20 antibodies were further assessed for rHuPH20-neutralizing activity using a validated in vitro hyaluronidase activity assay with a chromogenic readout (horseradish peroxidase and tetramethylbenzidine).

PopPK analysis

For the PopPK analysis, a patient was defined as evaluable if both of the following criteria were satisfied: patient received ≥1 dose of daratumumab SC; patient had ≥1 post-dose measurable daratumumab serum concentration with associated sampling time and dosing information. The PopPK dataset consisted of 1,224 measurable PK samples from 211 patients who received daratumumab SC. Twelve patients did not have any post-treatment serum daratumumab concentrations and were not included in the PopPK analysis. Data consisting of serum drug concentration below the LLOQ (BLOQ; 0.2 µg/mL) were kept in the analysis dataset and flagged accordingly. Nonlinear mixed-effects modeling software NONMEM® (Version 7.4), a software package for nonlinear mixed-effects analysis (Hanover, MD, USA), was used for PopPK modeling.

An exploratory analysis was performed on daratumumab dosing, serum concentration data, and potential covariates. Initially, a 2-compartment disposition model with first-order absorption, and parallel linear and nonlinear elimination pathways, which was previously used to describe PopPK analyses of daratumumab following IV or SC administrations in patients with multiple myeloma, was attempted to describe the serum concentration data.[27, 30, 31] However, the model was highly unstable on account of sparse PK samples in the current dataset, hence not enough data were available to

inform the initial distribution phase of a 2-compartment model. Thus, a 1-compartment disposition model with first-order absorption and parallel linear and nonlinear elimination pathways was adopted.[27]

Covariates of interest were included in the formal analysis and evaluated for statistical significance and clinical relevance. The evaluated covariates were available in >95% of patients. Tested covariates included body weight, sex, cardiac stage, renal stage, alkaline phosphatase (ALP), renal function, and hepatic function. In the first step of covariate evaluation, univariate tests were conducted for all candidate relations. All relations that passed the significant level of 0.05 by the likelihood ratio test were included in the next stage of covariate evaluation. In the second step, the selection process was performed using a stepwise forward addition followed by a stepwise backward elimination. The likelihood ratio test was used to evaluate the significance of incorporating or removing fixed effects into the population model based on significance levels that were set a priori. For forward addition and backward elimination, significance levels of 0.05 and 0.01 were employed, respectively. Furthermore, clinical relevance was also considered. To evaluate the influence of covariates on the exposure to daratumumab SC, the exposure metrics were simulated using individual post hoc PK parameters from the final PK model with the scheduled dosing regimen from the ANDROMEDA study to compare daratumumab SC exposure in various subgroups.

E-R analyses

For the E-R analyses, a patient was defined as evaluable if both of the following criteria were satisfied: patient in either treatment arm must have ≥1 measurement of the efficacy or safety

endpoint of interest with associated sampling time; patient in the treatment arm with daratumumab SC must have individual PK parameter estimates from the PopPK analysis. The exposure metrics for E-R analysis were derived using predicted concentration-time profiles following the actual dosing information (R Version 3.6.0 or higher).

The E-R analyses were performed for efficacy and safety endpoints of interest. Efficacy endpoints evaluated included confirmed hematologic CR, major organ deterioration progression-free survival, overall best confirmed hematologic response rate, involved free light-chain response (achieving involved free light-chain ≤20 mg/L post-treatment), and difference between involved and uninvolved free light-chain response (achieving difference between involved and uninvolved free light-chain <10 mg/L post-treatment). Safety endpoints included overall and grade 3 or 4 incidences of organ disorder (including cardiac, renal, and urinary disorders), infections, infusion-related reactions, and cytopenia (including thrombocytopenia, anemia, neutropenia, and lymphopenia). For categorical variables, a linear logistic regression model was considered. When necessary, as indicated by the observed data, the nonlinear function using sigmoid maximum efficacy (E_{max}) was considered. The simulated exposure metrics based on the actual dosing regimen were used for the E-R analyses as follows: maximal trough concentration ($C_{trough,max}$) across the entire treatment course was selected for all efficacy endpoints. $C_{trough,max}$ and maximal peak concentration ($C_{peak,\ max}$) best described the data and provided the lowest and comparable Akaike Information Criterion values (897 versus 896). Considering that $C_{trough,max}$ has been consistently used as the exposure surrogate for daratumumab in previous E-R analyses for efficacy endpoints in patients with multiple myeloma, it was also selected as the main exposure metric in the current E-R analyses for efficacy endpoints in patients with light-chain amyloidosis. For major organ deterioration progression-free survival, both peak concentration

(C_{peak}) following the first dose ($C_{peak,first}$) and $C_{trough,max}$ were evaluated. Other exposure metrics were considered, including AUC; however, most of them were found to be highly correlated and were not further evaluated. For safety endpoints, $C_{peak,max}$ was selected for all safety events except for infusion-related reactions, for which $C_{peak,first}$ was used as infusion-related reactions were most prominent after first administration. Several relevant covariates, such as body weight, baseline neutrophils, and baseline hemoglobin, were explored for a few selected safety endpoints for their potential impact on the E-R relationship.

Model-based simulations were performed to evaluate the selected daratumumab SC dosing regimen in the ANDROMEDA study and whether adequate exposures were achieved in different body weight subgroups. The primary evaluation was the univariate E-R relationships, with the modeled response evaluated in the 5th, 25th, 50th (median), 75th, and 95th percentiles of the exposure values.

RESULTS

Analysis dataset

The PopPK dataset comprised 1,224 non-BLOQ PK samples from 211 patients (28 patients from the safety run-in phase and 183 patients from the randomized phase) who received daratumumab SC 1,800 mg. All patients included in the final analysis had measurable daratumumab concentrations post-treatment. Patient baseline demographics and disease covariates are summarized in **Table 1**.

PopPK of daratumumab SC

The observed concentration-time data of daratumumab SC were well described by a 1-compartment PopPK model with first-order absorption and parallel linear and nonlinear Michaelis-Menten elimination pathways. The parameter estimates of the final PopPK model resulting from covariate analysis are provided in **Supplementary Table S1**. Based on exploratory data analysis and initial model development, it was found that current PK data would unlikely provide sufficient information in estimating Michaelis-Menten constant (K_m) and IIV on maximum velocity of the saturable clearance process (V_{max}). Considering that the base PK model was modified from a previously developed final structural SC model and the similarity in the abundance of CD38 between multiple myeloma and light-chain amyloidosis patients,[35] K_m was fixed to the same value (2.56 μg/mL) as in previous estimated value in multiple myeloma patients, and IIV on V_{max} was fixed to have the same variance as that estimated in multiple myeloma patients. The estimated first-order absorption rate constant (K_a) was 0.773 day^{-1}, which was approximately 2.7-fold the estimated value in patients with multiple myeloma (K_a of 0.288 day^{-1}).[27] This difference in K_a values may be attributed to the difference in model structure and sampling frequency, as the PK model for multiple myeloma study was built with more frequently sampled data, and a 2-compartment model was used. Both the apparent volume of distribution and the estimated apparent clearance of daratumumab SC in patients with light-chain amyloidosis were similar to those in patients with multiple myeloma, after accounting for the absolute bioavailability. The model-derived geometric mean (CV%) half-life associated with linear elimination was 27.5 days (74%) based on the post hoc PK estimates, which appeared to be slightly longer than that in multiple myeloma patients (20.4 days [22.4%]).[27] The steady-state serum daratumumab concentration was achieved approximately 5 months after the start of treatment at the recommended dosing regimen. The goodness-of-fit plots revealed no

systemic bias (**Supplemental Fig. S1**). In general, there was good agreement between the predicted and observed daratumumab concentrations for the patients in this analysis.

Comparison of PK profiles in light-chain amyloidosis and multiple myeloma

Simulations were conducted for the typical PK profile after daratumumab SC 1,800 mg administration in patients with light-chain amyloidosis or patients with multiple myeloma based on the final PopPK model with the recommended dose regimen. Based on the simulation, the observed daratumumab trough concentration (C_{trough}) at C3D1 was similar between the two indications, although daratumumab SC provided slightly higher peak concentrations (C_{peak}) and C_{trough} of daratumumab in patients with light-chain amyloidosis compared to patients with multiple myeloma (**Fig. 1**).

E-R for efficacy

The E-R analysis for efficacy included 183 patients from the daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone arm and 193 patients from the bortezomib, cyclophosphamide, and dexamethasone arm.

Hematologic response

The relationship between daratumumab systemic exposure and overall best confirmed hematologic response was analyzed using the ordinal logistic regression model. Different exposure metrics were

tested as possible predictors for overall best confirmed hematologic response and compared using Akaike information criterion (AIC) to identify the most predictive exposure metric that would best describe the efficacy data (**Supplementary Table S2**). Among the tested systemic exposure metrics, $C_{trough,max}$ was selected as the main metric for E-R analysis for efficacy endpoints in patients with light-chain amyloidosis. $C_{trough,max}$ provided one of the two lowest AIC values observed and was consistent with exposure metrics used for E-R analysis for multiple myeloma patients. **Fig. 2A** presents the relationship between overall best confirmed hematologic response and $C_{trough,max}$. Daratumumab systemic exposure levels were generally consistent across patients who achieved hematologic CR, very good partial response, or partial response (PR). Patients who had no response had numerically lower median systemic exposure; however, the number of patients in this group was very small (<4%) and the response rate was not related to body weight. This observation suggests that daratumumab SC 1,800 mg provided adequate and consistent systemic exposure to the majority of patients with light-chain amyloidosis.

A nonlinear logistic regression model with E_{max} was performed for the E-R relationship for the binary response according to whether the complete response hematologic CR was achieved. Parameter estimates are presented in **Supplementary Table S3**. Analysis showed consistency between the model-predicted probability of hematologic CR and the 95% confidence interval (CI) of observed incidence rate hematologic CR across the range of $C_{trough,max}$ values (**Fig. 2B**). The simulation results were based on 1,000 simulations of the nonlinear logistic regression model. The observed response rates and 95% CIs were calculated based on data from the 4 quartiles of $C_{trough,max}$. Outcomes for patients in the treatment arm with daratumumab SC demonstrated improved hematologic CR rates across all exposure quartiles in comparison to outcomes of patients in the treatment arm without

daratumumab SC (hematologic CR rates of 42%, 58%, 60%, and 62% for the first to fourth quartiles in the treatment arm with daratumumab SC versus 19% for the treatment arm without daratumumab SC). The model-predicted rates of hematologic CR and the 95% CI were analyzed in the 5th, 25th, 50th, 75th, and 95th percentiles of $C_{trough,max}$, and a median response rate of >50% was predicted for the lowest exposure quartile, indicating that the daratumumab SC dose of 1,800 mg provided adequate exposure for the majority of patients.

Major organ deterioration progression-free survival

Major organ deterioration progression-free survival, defined as time to either hematologic progression, MOD (clinical manifestation of end-stage cardiac or renal failure), or death, whichever occurred first, was monitored in the 11.4 months of median follow-up. A total of 87 major organ deterioration progression-free survival events (43.5% of planned events) occurred, with 34 events in the treatment arm with daratumumab SC and 53 events in the treatment arm without daratumumab SC. An apparent improvement in major organ deterioration progression-free survival was observed in the majority of patients in the treatment arm with daratumumab SC, from the second quartile to the fourth quartile, regardless of the systemic exposure metrics (**Supplementary Fig. S2**). However, outcomes should be interpreted with caution due to the limited number of major organ deterioration progression-free survival events observed at the time of clinical cutoff. In general, the E-R analysis on major organ deterioration progression-free survival supported that the flat dose of daratumumab SC 1,800 mg provided adequate systemic exposure for the majority of patients.

To further analyze the relationship between daratumumab systemic exposure and improved survival rates, a Cox proportional hazard model was developed to establish the E-R relationships between major organ deterioration progression-free survival and daratumumab exposure using the exposure metrics $C_{trough,max}$ and $C_{peak,first}$. The model-predicted probabilities demonstrated benefits in major organ deterioration progression-free survival at 6 and 12 months in the treatment arm with daratumumab SC across all percentiles of $C_{trough,max}$ (5th, 25th, 50th, 75th, and 95th percentiles) compared to the treatment arm without daratumumab SC. Substantial improvement in the probabilities of major organ deterioration progression-free survival was predicted starting at a relatively low exposure percentile (i.e., 25th percentile) with limited further improvement as exposure increased, which supports the use of 1,800 mg flat dose daratumumab SC for the majority of patients.

Free light-chain biomarkers

The exposure-efficacy analyses, with $C_{trough,max}$ as the systemic exposure metric, were performed for involved free light-chain achieving ≤20 mg/L post-treatment and difference between involved and uninvolved free light-chain achieving <10 mg/L post-treatment. Elevated daratumumab $C_{trough,max}$ was associated with a statistically significant increase (P <0.001) in the probability of achieving involved free light-chain ≤20 mg/L post-treatment (**Supplementary Fig. S3**). The observed incidence of achieving involved free light-chain ≤20 mg/L post-treatment was 20.2% in the treatment arm without daratumumab SC and 58.7%, 71.7%, 73.3%, and 87.0%, respectively, in the 1st to 4th exposure quartiles of $C_{trough,max}$ in the treatment arm with daratumumab SC. Furthermore, elevated daratumumab $C_{trough,max}$ was associated with a statistically significant increase (P <0.001) in the

probability of achieving difference between involved and uninvolved free light-chain <10 mg/L post-treatment (**Supplementary Fig. S4**). The observed incidence of achieving difference between involved and uninvolved free light-chain <10 mg/L post-treatment in the treatment arm without daratumumab SC was 30.6% versus 60.9%, 63.0%, 57.8%, and 80.4% in the 1st to 4th exposure quartiles of $C_{trough,max}$, respectively, in the treatment arm with daratumumab SC. In general, the exposures of patients who achieved involved free light-chain ≤20 mg/L or difference between involved and uninvolved free light-chain <10 mg/L post-treatment were within similar ranges as those who did not achieve those parameters post-treatment, which suggests that daratumumab SC 1,800 mg dose provided adequate exposure to the majority of patients with light-chain amyloidosis.

E-R for safety

There was no apparent E-R relationship between daratumumab exposure and safety endpoints (i.e., organ disorders, infections, infusion-related reactions, and cytopenia) using the $C_{peak,first}$ as the predictor for infusion-related reactions and $C_{peak,max}$ for other endpoints (**Table 2**). Although clinical data showed that the incidence for neutropenia (as an AE) was 10.9% in the treatment arm with daratumumab SC and 6.4% in the treatment arm without daratumumab SC, there was no statistically significant relationship between neutropenia and daratumumab systemic exposure. Additional E-R analyses for neutropenia and infections and infestations endpoints were performed using logistic regression, with potential confounding effects adjusted by covariates of clinical interest, such as body weight, baseline neutrophils, and hemoglobin. Results showed that there was no statistically significant relationship between daratumumab exposure and the incidence of neutropenia (P = 0.0513). The E-R relationship was statistically significant for infections and infestations (P = 0.006);

however, the slope of the increased probability of infections with increasing exposure was small (0.000689) and was unlikely to be clinically relevant (**Fig. 3**).

Effect of covariates

A covariate analysis was performed to assess the impact of intrinsic factors on the PK profile of daratumumab SC in patients with light-chain amyloidosis (**Supplementary Fig. S5**). All covariates of interest were tested for their potential impact on the exposure of daratumumab SC. Body weight and renal stage were identified as statistically significant covariates on apparent nonspecific CL/F. Body weight, renal stage, and alkaline phosphatase (ALP) were identified as statistically significant covariates on the apparent volume of distribution. However, outcomes from model simulation demonstrated that the effects of the investigated intrinsic factors had no clinically meaningful impact on daratumumab exposure.

Similar efficacy in terms of hematologic CR rate was observed across the various subgroups, with an exception for renal stage III. Comparison between patients with renal stage I (*n* = 117) versus patients with renal stage II (*n* = 74) suggest that hematologic CR rate was not correlated with daratumumab exposure (71.4% for patients with renal stage II; 51.3% for patients with renal stage I). Numerically lower (27%) geometric mean daratumumab exposure was observed for patients with renal stage III; however, this difference in exposure between renal stage groups should be interpreted with caution due to the small sample size of patients with renal stage III (*n* = 17) and overlapping exposure CI between renal stage III and stage II. Although patients with baseline proteinuria >5 g/24 hr had lower predicted C_{trough} than patients with baseline proteinuria ≤5 g/24 hr, clinical efficacy analysis showed that efficacy in terms of hematologic CR rate did not appear to be

related with daratumumab exposure (63.9% for patients with baseline proteinuria >5 g/24 hr; 48.5% for patients with baseline proteinuria ≤5 g/24 hr). The simulated PK profiles in patients with or without hematologic CR were comparable during the treatment course, including after C3.

Treatment-emergent ADAs were not observed in the ANDROMEDA study and were not evaluated for PK impact. The following factors had neither statistically significant nor clinically relevant effect on the exposure of daratumumab: sex, race, age, cardiac stage, renal function, hepatic function, baseline Eastern Cooperative Oncology Group (ECOG) performance status, and anti-rHuPH20 status.

Influence of body weight on efficacy and safety

Baseline body weight was evaluated as a predictor of hematologic CR rate in overall best confirmed hematologic response in the treatment arm with daratumumab SC compared to the treatment arm without daratumumab SC. Results showed that baseline body weight was not a significant predictor of hematologic CR either in patients treated with daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone (P = 0.99) or in patients treated with bortezomib, cyclophosphamide, and dexamethasone alone (P = 0.217; **Supplementary Fig. S6**). The observed increase in hematologic CR with increasing body weight in the treatment arm without daratumumab SC had no significant relationship. Notably, there were 5 patients with body weight >120 kg (3 patients in the treatment arm with daratumumab SC; 2 patients in the treatment arm without daratumumab SC). Among these patients, those who received daratumumab plus bortezomib, cyclophosphamide, and dexamethasone responded well, with 2 of 3 patients achieving hematologic CR, while none achieved hematologic CR in the treatment arm without daratumumab SC.

In patients in the treatment arm with daratumumab SC, the rate of neutropenia decreased significantly with increasing baseline body weight (P = 0.0031), while those in the treatment arm without daratumumab SC showed no apparent body weight dependence (P = 0.902). Logistic regression was performed to further investigate the relationship between neutropenia and daratumumab exposure with body weight, $C_{peak,max}$, baseline neutrophil, and baseline hemoglobin count as covariates. Body weight (P = 0.0168) was the only statistically significant predictor among the 4 evaluated covariates in the treatment arm with daratumumab SC (**Supplementary Table S4**). There was no apparent relationship between the incidence of neutropenia and daratumumab exposure after adjusting for the body weight effect (P = 0.0513). In the treatment arm without daratumumab SC, among the analyzed predictors (body weight, baseline neutrophil, and baseline hemoglobin counts), hemoglobin level was identified as the only significant predictor (P = 0.0448).

Furthermore, the rates of lymphopenia and infections and infestations were analyzed in relation to baseline body weight. No significant correlation was identified between body weight and the incidence of lymphopenia in patients treated with daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone (P = 0.31) or bortezomib, cyclophosphamide, and dexamethasone alone (P = 0.749). Logistic regression performed for lymphopenia with body weight and $C_{peak,max}$ showed no apparent relationship between lymphopenia rates and daratumumab systemic exposure (P = 0.382). In terms of rates of infections and infestations in relation to body weight, no significant correlation was identified (P = 0.412) in the treatment arm with daratumumab SC, while a significant decrease in infections and infestations was observed in the treatment arm

without daratumumab SC as body weight increased (P = 0.0193). Logistic regression was performed for infections and infestations in the treatment arm with daratumumab SC with body weight, $C_{peak,max}$, baseline neutrophil, and baseline hemoglobin counts as potential predictors, none of which showed statistical significance. In the treatment arm without daratumumab SC, logistic regression performed with body weight, baseline neutrophil, and baseline hemoglobin counts as the predictors identified body weight as the only statistically significant predictor (P = 0.0294).

Overall, no dose adjustment is recommended for patients based on body weight because the impact of body weight on daratumumab exposure was limited, and within the observed range, daratumumab exposures did not significantly impact the efficacy or safety outcomes.

DISCUSSION

These PopPK and E-R results support the selected daratumumab SC 1,800 mg dose regimen for the treatment of light-chain amyloidosis. Initially, a 2-compartment PopPK model with first-order absorption and parallel linear and nonlinear Michaelis-Menten elimination pathways was tested to describe the observed concentration-time data of daratumumab after daratumumab SC administration, which was the same structural model used to describe daratumumab SC PopPK in multiple myeloma patients. However, the model was highly unstable on account of sparse PK samples in the current dataset for light-chain amyloidosis. Thus, a 1-compartment disposition model with first-order absorption and parallel linear and nonlinear elimination pathways was used in this analysis as opposed to a 2-compartment disposition model used for multiple myeloma. In

comparison to patients with multiple myeloma (who also received daratumumab SC), daratumumab SC 1,800 mg administration provided slightly higher model-predicted C_{peak} and C_{trough} in patients with light-chain amyloidosis, although the concentration was generally in the same range.

Among patients included in the assessment for E-R relationship for efficacy, daratumumab SC 1,800 mg flat dose resulted in generally consistent exposure levels across patients who achieved hematologic CR, very good partial response, or PR. The results also showed that the E_{max} of daratumumab as measured by hematologic CR rate was achieved by the majority of patients with daratumumab SC 1,800 mg. In terms of major organ deterioration progression-free survival, a substantial improvement in major organ deterioration progression-free survival results was observed in patients in the treatment arm with daratumumab SC compared to those in the treatment arm without daratumumab SC. In addition, the systemic exposure measured by $C_{trough,max}$ showed consistency across patients who did or did not achieve involved free light-chain ≤20 mg/L or difference between involved and uninvolved free light-chain <10 mg/L post-treatment. Furthermore, there was no apparent E-R relationship between daratumumab exposure and safety endpoints (organ disorders, infections, infusion-related reactions, and cytopenia). Overall, results suggest that daratumumab SC 1,800 mg dose provided adequate systemic exposure to the majority of patients with light-chain amyloidosis and that no dose adjustment is required.

A covariate analysis was performed to assess the impact of intrinsic factors on the PK profile of daratumumab SC. Although body weight, renal stage, and baseline ALP were identified to be significant covariates on the daratumumab PopPK model, simulation demonstrated that magnitudes

of those effects on the systemic exposure of daratumumab were small. Efficacy assessed by hematologic CR rate was similar across the subgroups, except for results in the renal stage III group. It should also be noted that renal stage was correlated with baseline proteinuria and creatinine clearance. Clinical efficacy analysis showed that the efficacy in terms of hematologic CR rate does not appear to be related to daratumumab exposure. In addition, PopPK simulations showed no clinically important differences in exposure to daratumumab between patients with moderate or severe renal impairment (categorized by creatinine clearance) (C3D1 C_{trough} [95% CI]: 655 [597, 717] µg/mL) and those with normal renal function (C3D1 C_{trough} [95% CI]: 567 [527, 610] µg/mL). With the potential concern of lower exposure in patients with body weight >85kg and renal stage III, further analysis was performed to evaluate whether dose adjustments would be needed for this special subpopulation. Among the seven patients who had baseline body weight >85kg and renal stage III in this study, two of them were in the daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone arm. Both observed and predicted individual daratumumab concentrations from these two patients were within the range for those from the rest of the patients, suggesting that patients with body weight >85kg and renal stage III still appear to have adequate daratumumab exposure for the desired treatment benefits, and thus no dose adjustment would be needed. However, no definitive conclusion can be drawn with regards to the hematologic response due to the small sample size.

The following factors had neither statistically significant nor clinically relevant effect on the exposure of daratumumab: sex, race, age, cardiac stage, renal function, hepatic function, baseline ECOG status, and anti-rHuPH20 status. Treatment-emergent ADAs were not observed in the ANDROMEDA study and were not evaluated for PK impact. Overall, the effects of the investigated intrinsic factors

on daratumumab exposure had no clinically meaningful impact on study outcomes, and dose adjustment based on these factors is not recommended.

Baseline body weight was evaluated as a predictor of hematologic CR rate, and results show that baseline body weight is not a significant predictor of hematologic CR in either treatment arm. In terms of the relationship between neutropenia and daratumumab systemic exposure, body weight was the only statistically significant predictor among the identified covariates (body weight, $C_{peak,max}$, baseline neutrophil, and baseline hemoglobin counts). Results show that there was no apparent relationship between the incidence of neutropenia and daratumumab systemic exposure after adjusting for the body weight effect on neutropenia.

CONCLUSIONS

In conclusion, in patients with light-chain amyloidosis, daratumumab SC plus bortezomib, cyclophosphamide, and dexamethasone showed a comparable PK profile to daratumumab SC, both as monotherapy and combination therapies, in patients with multiple myeloma. Daratumumab SC 1,800 mg provided adequate and consistent systemic exposure to the majority of patients with light-chain amyloidosis, and there was no apparent relationship between daratumumab systemic exposure and safety endpoints. Although patients with baseline proteinuria >5 g/24 hr had lower predicted C_{trough}, efficacy does not appear to be related with daratumumab exposure. Therefore, the effect of proteinuria on daratumumab exposure had no clinically meaningful impact on study outcomes, consistent with other factors investigated. Despite the increased neutropenia with decreasing body weight, no meaningful clinical consequences such as increased infections or

discontinuations were observed. These data support the use of daratumumab SC 1,800 mg flat dose in combination with bortezomib, cyclophosphamide, and dexamethasone for the treatment of light-chain amyloidosis.

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DATA AVAILABILITY

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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FIGURE LEGENDS

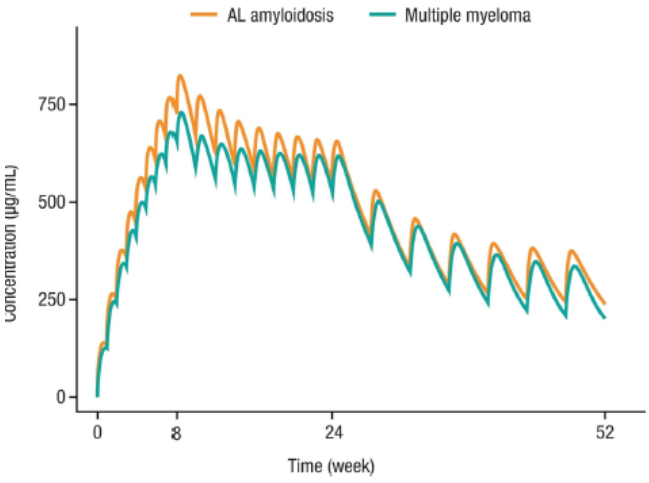

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Figure 1. Typical PK profile of daratumumab after daratumumab SC 1,800 mg in patients with light-chain amyloidosis or in patients with multiple myeloma

PK, pharmacokinetic; SC, subcutaneous.

Note: The approved dose schedule for daratumumab in patients with multiple myeloma consisted of weekly administration for 8 weeks (8 doses), every 2 weeks for 16 weeks (8 doses), and every 4 weeks thereafter.

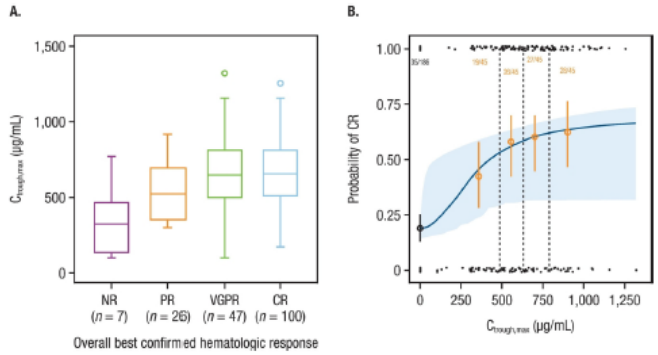

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Figure 2. Relationship between overall best confirmed hematologic response and $C_{trough,max}$. (A) Box plot for predicted daratumumab $C_{trough,max}$ for different categories of overall best confirmed hematologic response after daratumumab SC 1,800 mg plus bortezomib, cyclophosphamide, and dexamethasone and (B) E_{max} relationship between predicted daratumumab $C_{trough,max}$ and CR.

$C_{trough,max}$, maximal trough concentration; SC, subcutaneous; E_{max}, maximum efficacy; CR, complete response; NR, not reached; PR, partial response; VGPR, very good partial response.

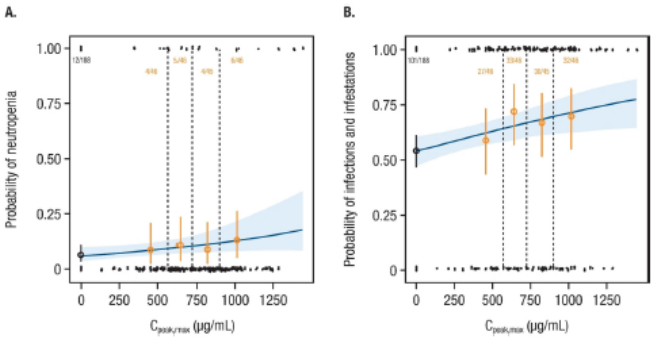

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Figure 3. E-R analyses for neutropenia and infections and infestations. Exposure safety relationships for (A) neutropenia and (B) infections and infestations.

E-R, exposure-response; $C_{peak,max}$, peak concentration; CI, confidence interval.

Notes: The solid blue line is the logistic regression fit using binomial logit function. The light blue band represents the 95% CI of the fit. Black dots at probabilities of 0 and 1 represent the observed neutropenia (**A**) and infections and infestations (**B**) responses. Patients are stratified into daratumumab $C_{peak,max}$ quartiles: 1st quartile (≤570 μg/mL), 2nd quartile (571–722 μg/mL, 3rd quartile (723–898 μg/mL), and 4th quartile (899–1450 μg/mL). The black, vertical dashed lines separate the quartiles of $C_{peak,max}$. Orange points are mean exposure and neutropenia rate per quartile (left panel) or infections and infestations rate (right panel), and the black point is the neutropenia rate (left panel) and infections and infestations rate (right panel) in the control (bortezomib, cyclophosphamide, and dexamethasone alone) arm. Vertical orange or black bars crossing the points are the 95% CIs of the neutropenia (left panel) and infections and infestations (right panel) rate.

Table 1. Patient Baseline Demographics and Disease Covariates

Parameter	**PopPK population** ***n*** **= 211**	**Patients who received bortezomib, cyclophosphamide, and dexamethasone alone** ***n*** **= 188**
Sex		
Female	95 (45.0)	73 (38.8%)

Male	116 (55.0)	115 (61.2%)
Body mass, kg		
Mean (SD)	74.2 (16.4)	73.5 (17.5)
Median [min, max]	73.2 [41.5, 142.0]	70.1 [38.0, 135.0]
Lean body mass, kg		
Mean (SD)	53.5 (10.7)	53.5 (10.7)
Median [min, max]	52.4 [32.5, 86.2]	52.9 [30.9, 83.4]
Body mass category, kg/m^2		
≤65	61 (28.9)	72 (38.3)
>65–≤85	103 (48.8)	71 (37.8)
>85	47 (22.3)	45 (23.9)
Serum creatinine, µM (normal value: <133 µM)		
Mean (SD)	94.2 (40.0)	101 (45.7)
Median [min, max]	84.0 [35.0, 239.0]	88.0 [37.0, 249.0]
CrCL, mL/min (normal values: male, 97 to 137 mL/min; female, 88 to 128 mL/min)		
Mean (SD)	81.0 (39.5)	74.8 (35.8)
Median [min, max]	76.2 [21.6, 238.0]	73.5 [19.4, 286.0]
eGFR, mL/min/1.73 m^2 (normal value: ≥90 mL/min/1.73 m^2)		
Mean (SD)	73.6 (25.5)	70.6 (25.8)
Median [min, max]	79.0 [21.1, 126.0]	76.0 [19.8, 121.0]

eGFR category, eGFR mL/min		
≥15–<30	15 (7.1)	21 (11.2)
≥30–<60	50 (23.7)	40 (21.3)
≥60–<90	79 (37.4)	74 (39.4)
≥90	67 (31.8)	53 (28.2)
Renal function, CrCL mL/min		
≥15–<30	10 (4.7)	19 (10.1)
≥30–<60	59 (28.0)	42 (22.3)
≥60–<90	67 (31.8)	76 (40.4)
≥90	75 (35.5)	51 (27.1)
Total protein, g/L (normal value: 55-80 g/L)		
Mean (SD)	60.5 (12.2)	61.0 (12.3)
Median [min, max]	61.0 [33.0, 104.0]	61.5 [34.0, 119.0]
Baseline proteinuria, g/24 hr (normal value: <0.15 g/24 hr)		
Mean (SD)	3.73 (4.77)	4.10 (5.15)
Median [min, max]	1.74 [2.69e-05, 26.2]	2.10 [0, 21.0]
Baseline proteinuria category		
Missing	3 (1.4)	0 (0)
Proteinuria ≤5 g/24 hr	143 (67.8)	170 (90.4)
Proteinuria >5 g/24 hr	65 (30.8)	18 (9.6)
Cardiac stage group		

Stage I	49 (23.2)	42 (22.3)
Stage II	88 (41.7)	79 (42.0)
Stage III	74 (35.1)	67 (35.6)
Renal stage group		
Stage I	117 (55.5)	97 (51.6)
Stage II	74 (35.1)	73 (38.8)
Stage III	17 (8.1)	18 (9.6)
Missing	3 (1.4)	0 (0)
Hepatic dysfunction level		
Mild dysfunction	42 (19.9)	37 (19.7)
Moderate dysfunction	3 (1.4)	2 (1.1)
Normal	166 (78.7)	149 (79.3)
Baseline ALP		
Abnormal	15 (7.1)	15 (8.0)
Missing	1 (0.5)	0 (0)
Normal	195 (92.4)	173 (92.0)
Treatment-emergent anti-rHuPH20 antibody		
No	176 (83.4)	–
Unevaluable	8 (3.8)	–
Yes	27 (12.8)	–
Baseline anti-rHuPH20 antibody		
No	181 (85.8)	–

Unevaluable	3 (1.4)	–
Yes	27 (12.8)	–
Treatment-emergent anti-daratumumab antibody		
No	190 (90.0)	–
Unevaluable	21 (10.0)	–
Baseline anti-daratumumab antibody		
No	199 (94.3)	–
Unevaluable	12 (5.7)	–

PopPK, population pharmacokinetics; SD, standard deviation; min, minimum; max, maximum; CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; ALP, alkaline phosphatase; rHuPH20, recombinant human hyaluronidase PH20.

Note: Values are number (%) unless otherwise stated. Normal laboratory values from labcorp.com[36] and Kratz 2004[37]

Table 2. Incidence Rate by Daratumumab Systemic Exposure Quartile for Safety Endpoints

Safety endpoint	**Bortezomib, cyclophosphamide, and dexamethasone alone, % (95% CI) (*n* = 188)**	**Daratumumab SC plus bortezomib, cyclophosphamide, ar exposure quartiles, % (95% CI)**		
		1st (*n* = 46)	**2nd (*n* = 46)**	**3rd (*n* = 45)**

Infusion-related reactions	–	8.7 (2.4–20.8)	8.7 (2.4–20.8)	0 (0–7.9)
Grade ≥3	–	0 (0–7.7)	0 (0–7.7)	0 (0–7.9)
Neutropenia	6.4 (3.3–10.9)	8.7 (2.4–20.8)	10.9 (3.6–23.6)	8.9 (2.5–21.2)
Grade ≥3	2.7 (0.9–6.1)	4.3 (0.5–14.8)	4.3 (0.5–14.8)	4.4 (0.5–15.1)
Anemia	23.4 (17.6–30.1)	21.7 (10.9–36.4)	26.1 (14.3–41.1)	20.0 (9.6–34.6)
Grade ≥3	4.8 (2.2–8.9)	6.5 (1.4–17.9)	6.5 (1.4–17.9)	0 (0–7.9)
Thrombocytopenia	11.7 (7.5–17.2)	10.9 (3.6–23.6)	26.1 (14.3–41.1)	15.6 (6.5–29.5)
Grade ≥3	2.7 (0.9–6.1)	2.2 (0.1–11.5)	6.5 (1.4–17.9)	0 (0–7.9)
Lymphopenia	14.9 (10.1–20.8)	10.9 (3.6–23.6)	23.9 (12.6–38.8)	20.0 (9.6–34.6)
Grade ≥3	10.1 (6.2–15.3)	6.5 (1.4–17.9)	15.2 (6.3–28.9)	15.6 (6.5–29.5)
Infections and infestations	53.7 (46.3–61.0)	58.7 (43.2–73.0)	71.7 (56.5–84.0)	66.7 (51.0–80.0)
Grade ≥3	10.1 (6.2–15.3)	23.9 (12.6–38.8)	23.9 (12.6–38.8)	8.9 (2.5–21.2)
Cardiac disorder	21.8 (16.1–28.4)	34.8 (21.4–50.2)	26.1 (14.3–41.1)	22.2 (11.2–37.1)
Grade ≥3	9.6 (5.8–14.7)	13.0 (4.9–26.3)	10.9 (3.6–23.6)	6.7 (1.4–18.3)
Renal and urinary disorder	18.1 (12.9–24.3)	21.7 (10.9–36.4)	17.4 (7.8–31.4)	24.4 (12.9–39.5)
Grade ≥3	6.4 (3.3–10.9)	10.9 (3.6–23.6)	0 (0–7.7)	8.9 (2.5–21.2)

CI, confidence interval; SC, subcutaneous; $C_{peak,first}$, peak concentration following the first dose; $C_{peak,max}$, peak concentration.

Notes: $C_{peak,first}$ was used as the exposure measure for analyses on infusion-related reactions, while $C_{peak,max}$ was used as the exposure measure for analyses on other adverse events.

The quartiles for $C_{peak,first}$ were as follows: 1st quartile (≤122 μg/mL), 2nd quartile (123–153 μg/mL), 3rd quartile (154–183 μg/mL), and 4th quartile (184–417 μg/mL).

The quartiles for $C_{peak,max}$ were as follows: 1st quartile (≤570 μg/mL), 2nd quartile (571–722 μg/mL), 3rd quartile (723–898 μg/mL), and 4th quartile (899–1,450 μg/mL).