Received: 15 April 2022 | Revised: 14 October 2022 | Accepted: 20 November 2022

DOI: 10.1111/bcp.15628

ORIGINAL ARTICLE

Population pharmacokinetics and exposure–response analyses of daratumumab plus pomalidomide/dexamethasone in relapsed or refractory multiple myeloma

Anne-Gaelle Dosne[1] | Xia Li[1] | Man Melody Luo[2] | Ivo Nnane[2] | Meletios A. Dimopoulos[3] | Evangelos Terpos[3] | Pieter Sonneveld[4] | Tobias Kampfenkel[5] | Robin Carson[6] | Himal Amin[7] | Juan Perez Ruixo[8] | Honghui Zhou[2,9] | Yu-Nien Sun[2,10] | Yan Xu[2,11]

[1]Clinical Pharmacology and Pharmacometrics, Janssen Research & Development, LLC, Beerse, Belgium

[2]Clinical Pharmacology and Pharmacometrics, Janssen Research & Development, LLC, Spring House, Pennsylvania, USA

[3]National and Kapodistrian University of Athens, Athens, Greece

[4]Erasmus University Medical Center Cancer Institute, Rotterdam, The Netherlands

[5]Janssen Research & Development, LLC, Leiden, The Netherlands

[6]Janssen Research & Development, LLC, Spring House, Pennsylvania, USA

[7]Janssen Research & Development, LLC, Raritan, New Jersey, USA

[8]Janssen-Cilag Spain, Part of Janssen Pharmaceutical Companies, Madrid, Spain

[9]Kira Pharmaceuticals, Cambridge, Massachusetts, USA

[10]Cognigen Division, Simulations-Plus Company, Buffalo, New York, USA

[11]Simcere Pharmaceuticals, Cambridge, Massachusetts, USA

Correspondence
Anne-Gaelle Dosne and Xia Li, Clinical Pharmacology and Pharmacometrics, Janssen EMEA, Turnhoutseweg 30, 2340, Beerse, Belgium.
Email: adosne@its.jnj.com and xli120@its.jnj.com

Present address
Honghui Zhou, Kira Pharmaceuticals, Cambridge, Massachusetts, USA.

Yu-Nien Sun, Cognigen Division, Simulations-Plus Company, Buffalo, New York, USA.

Yan Xu, Simcere Pharmaceuticals, Cambridge, Massachusetts, USA.

Funding information
European Myeloma Network; Janssen Research & Development, LLC; Janssen Global Services, LLC

Aim: A population pharmacokinetic (PPK) model was developed to characterize pharmacokinetics (PK) of subcutaneous or intravenous daratumumab administration in a new indication (i.e., combination with pomalidomide and dexamethasone [D-Pd] in patients with relapsed or refractory multiple myeloma [RRMM]). Analyses were conducted to explore exposure–response (E-R) relationships for efficacy and select treatment-emergent adverse events (TEAEs).

Methods: The PPK analysis included pooled data from the D-Pd cohorts of the phase 3 APOLLO and phase 1b EQUULEUS studies. Covariates were evaluated in the PPK model. Model-predicted exposures to daratumumab were compared between covariate subgroups of interest and used to investigate relationships between daratumumab exposure and efficacy and safety in APOLLO.

Results: The PPK analysis included 1146 daratumumab PK samples from 239 patients (APOLLO, $n = 140$; EQUULEUS, $n = 99$). Observed concentration–time data of daratumumab were well described by a two-compartment PPK model with first-order

There is no Principal Investigator for the described population modelling analysis; the clinical study and data have been published elsewhere, as described in this manuscript.

absorption and parallel linear and nonlinear elimination pathways. Treatment with D-Pd provided similar daratumumab PK characteristics versus historical daratumumab monotherapy. The E-R dataset contained data from 290 APOLLO patients (D-Pd, $n = 140$; Pd, $n = 150$). The PK–efficacy relationship of daratumumab supported improved progression-free survival for patients in the D-Pd group *vs.* the Pd group. Additionally, TEAEs did not increase with increasing PK exposure in the D-Pd group.

Conclusions: The PPK and E-R analyses support the daratumumab subcutaneous 1800 mg dosing regimen in combination with Pd for treatment of patients with RRMM. No dose adjustment is recommended in this indication for any of the investigated factors, none of which had clinically relevant effects on daratumumab PK.

KEYWORDS

exposure–response, multiple myeloma, onco-haematology, pharmacokinetics, population analysis

1 | INTRODUCTION

Multiple myeloma (MM) is a haematologic malignancy characterized by abnormal proliferation of clonal plasma cells.[1] MM is a heterogeneous disease and, while early stages are asymptomatic, progression lowers resistance to infection; causes skeletal damage; and leads to hypercalcaemia, renal failure, anaemia and osteolytic lesions.[2,3] While standard of care has evolved and has offered improvements in overall survival, the majority of MM patients will eventually fail to respond to current treatments.[4]

Daratumumab is a human IgGκ monoclonal antibody (mAb) targeting **CD38** with a direct on-tumour[5–8] and immunomodulatory[9–11] mechanism of action. The pharmacokinetics (PK) of intravenously (IV) administered daratumumab monotherapy were evaluated in patients with relapsed or refractory MM (RRMM) at dose levels from 0.1 to 24 mg/kg.[12] Peak serum concentrations (C_{max}) after first administration increased in approximate proportion to dose, and volume of distribution was consistent with initial distribution into the plasma compartment. After multiple doses, C_{max} and area under the concentration–time curve increased in a more than dose-proportional manner, and terminal half-life increased with increasing dose. A population pharmacokinetic (PPK) model of daratumumab indicated that clearance of daratumumab was both concentration- and time-dependent, which may be related to the saturation of a target-mediated disposition process and tumour burden decreases over time, respectively.[13] The estimated elimination half-life associated with linear clearance (CL) was approximately 15–24 days.[14] The covariates found to have a statistically significant but not clinically relevant effect of daratumumab PK included body weight, albumin concentration, type of myeloma (IgG *vs.* non-IgG) and sex.[15]

Subcutaneously administered daratumumab (daratumumab SC; daratumumab 1800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA]) was developed to reduce the burden for patients and providers and is approved for the treatment of MM.[16,17] A PPK study was performed to describe the PK characteristics of daratumumab SC monotherapy and combination therapy.[14] With an estimated bioavailability of 0.69, which is consistent with other mAbs subcutaneously co-administered with rHuPH20,[18,19] the approved daratumumab SC 1800 mg dose provided smaller

What is already known about this subject

- Daratumumab is a human IgGκ monoclonal antibody targeting CD38, a transmembrane glycoprotein overexpressed in multiple myeloma (MM) cells, that is approved throughout the world to treat adult MM as monotherapy and various combination therapies.
- Population pharmacokinetic (PK) models using intravenous (IV) and subcutaneous (SC) formulations were developed in these indications.

What this study adds

- The PK profile of daratumumab IV or SC plus pomalidomide/dexamethasone (Pd) was consistent with daratumumab monotherapy.
- Daratumumab PK–efficacy/–safety relationships support improved progression-free survival in most (75%) MM patients who received Pd without increased adverse event incidence with increasing exposure.
- No daratumumab SC dose adjustment is recommended for these patients.

peak-to-trough fluctuations, lower C_{max} and higher trough concentrations (C_{trough}) throughout the dose schedule compared with the approved daratumumab IV 16 mg/kg dosing regimen.[14] Overall, the range of exposures across all daratumumab SC studies fell within the exposure range observed in the daratumumab IV programme. Additionally, the daratumumab SC 1800 mg dose was shown to be noninferior to the 16 mg/kg IV dose in terms of efficacy and PK, with an improved safety profile, in a previous phase 3 study.[20]

Previous exposure–response (E-R) analysis suggested that daratumumab efficacy was significantly correlated with daratumumab exposures, and the maximum C_{trough} ($C_{trough,max}$), typically achieved at Cycle 3 Day 1 pre-dose, had the strongest correlation with efficacy endpoints among the investigated exposure metrics.[16,21] Examination of relationships between efficacy and model-predicted $C_{trough,max}$ suggested a similar E-R between daratumumab SC and daratumumab IV. The E-R analysis also suggested that daratumumab exposure after SC or IV dosing had no apparent correlation with selected safety endpoints, such as infusion-related reactions (IRRs), other serious adverse events and treatment-emergent adverse events (TEAEs).[14]

Daratumumab is approved in combination with pomalidomide and dexamethasone (D-Pd) for patients with RRMM.[22,23] Given the encouraging clinical benefit,[24,25] it is important to understand daratumumab PK in the D-Pd combination and the relationship between daratumumab model-predicted exposure and both efficacy and safety in patients receiving D-Pd. In this report, PPK analyses were conducted using data from two combination studies (i.e., the phase 3 APOLLO study and the phase 1b EQUULEUS study [D-Pd cohort]), where effects of patient- and disease-related factors on PK were assessed. The E-R relationships for key efficacy and safety endpoints were explored using data from the pivotal APOLLO study.

2 | METHODS

2.1 | Patients and study design

The PPK analysis included serum concentrations of daratumumab from APOLLO (ClinicalTrials.gov Identifier, NCT03180736) and EQUULEUS (ClinicalTrials.gov Identifier, NCT01998971) D-Pd cohorts.[24,25] The E-R analysis for efficacy and safety was based on data from APOLLO only (D-Pd and pomalidomide and dexamethasone [Pd] cohorts). Key study design elements and PK sampling are provided in Table 1. Independent ethics or institutional review boards at each site approved the protocols. The trials were conducted in accordance with the Declaration of Helsinki principles and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent. The APOLLO study was sponsored by the European Myeloma Network in collaboration with Janssen Research & Development, LLC. The EQUULEUS study was sponsored by Janssen Research & Development, LLC. Baseline patient demographic and disease characteristics are described in Table 2.

2.2 | Bioanalytical assays

An enzyme-linked immunosorbent assay (Janssen Research & Development, LLC, Spring House, PA, USA) was used to determine daratumumab concentrations in human serum samples, as previously described.[14] The lower limit of quantification for daratumumab was 0.2 μg/mL, and the calibration range was 0.2–5832 μg/mL.

TABLE 1 Overview of studies and data included in the PPK and exploratory E-R analysis

Study	Study title and design	Brief description of PK and efficacy/safety data
APOLLO ongoing	A randomized, open-label, phase 3 study comparing pomalidomide and dexamethasone with or without daratumumab in patients aged ≥18 years with relapsed or refractory MM who had received ≥1 prior line of therapy with both lenalidomide and a PI. Patients had an ECOG PS of 0–2, at least a partial response to ≥1 previous lines of antimyeloma therapy, and were refractory to lenalidomide if they had received only 1 previous line of therapy.[25] **Daratumumab (D-Pd patients):** Doses: 1800 mg SC or 16 mg/kg IV Dose schedule: QW for Cycles 1 and 2, then Q2W for Cycles 3–6, and then Q4W thereafter. A cycle is 28 days **Pomalidomide (all patients):** Doses and dose schedule: 4 mg PO on Days 1–21 of each cycle **Dexamethasone (all patients):** Doses: 40 mg (20 mg for patients aged ≥75 years) PO Dose schedule: Once daily on Days 1, 8, 15 and 22 of each cycle. Split IV/PO for 40 mg dose when together with daratumumab[a]	299 randomized and treated patients; D-Pd: $n = 149$, Pd: $n = 150$ **PK-evaluable patients ($n = 140$)** Patients on daratumumab SC only: $n = 133$ Sampling: C1D1 + 4, C3D1 + 4, C5-C7-C12D1 Patients switched from daratumumab IV to SC: $n = 4$ Sampling: SC pre-dose first 3 cycles (starting with C3 or later) + 2 FU (possible each cycle D1 after C3) Patients on daratumumab IV only: $n = 3$ Sampling: C1D1 pre-dose, C1D1 EOI, C3D1, C7D1, 4 and 8 weeks after last dose **Efficacy:** Primary endpoint: PFS **Safety:** Safety was a secondary endpoint. Monitoring for TEAEs took place continuously throughout the study

(Continues)

TABLE 1 (Continued)

Study	Study title and design	Brief description of PK and efficacy/safety data
EQUULEUS (D-Pd cohort)	An open-label, multicentre, phase 1b study of daratumumab in combination with backbone regimens for the treatment of patients aged ≥18 years with MM (newly diagnosed or those who had received prior therapies, depending on the background treatment regimen). Patients had an ECOG PS of 0–2; previously treated patients had received ≥2 prior lines of antimyeloma therapy, including ≥2 consecutive cycles of prior treatment that included lenalidomide and bortezomib. Lenalidomide-refractory patients were eligible.[24] **Daratumumab:** Doses: 16 mg/kg IV Dose schedule: QW for Cycles 1 and 2, then Q2W for Cycles 3–6, and then Q4W thereafter. A cycle is 28 days **Pomalidomide:** Doses and dose schedule: 4 mg PO once daily on Days 1–21 of each cycle **Dexamethasone:** Doses: 40 mg (20 mg for patients aged ≥75 years) PO Dose schedule: Once daily on Days 1, 8, 15 and 22 of each cycle. Split IV/PO when together with daratumumab	103 patients receiving D-Pd **PK evaluable patients ($n = 99$)** Sampling: C1–C4D1, C1D22 pre-dose + EOI + 2 FU (Weeks 3 and 9) **Efficacy:** Overall response rate was a secondary endpoint **Safety:** Safety was a primary endpoint. Monitoring for TEAEs took place continuously throughout the study Note that this study was pooled with APOLLO for the PPK analysis, but was not used for the E-R analysis

Abbreviations: C, Cycle; D, Day; FU, follow-up; D-Pd, daratumumab SC or IV in combination with pomalidomide and dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; EOI, end-of-infusion; E-R, exposure—response; IV, intravenous; MM, multiple myeloma; Pd, pomalidomide and dexamethasone; PI, proteasome inhibitor; PK, pharmacokinetics; PO, oral; PPK, population pharmacokinetics; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event.

[a]During the weeks when the patients receive daratumumab, 20 mg dexamethasone was administered IV on the day of infusion as the pre-infusion medication and the remaining 20 mg self-administered PO the following day.

TABLE 2 Descriptive statistics of the PPK dataset (baseline continuous and categorical covariates)

	EQUULEUS ($n = 99$)	APOLLO ($n = 140$)	Combined ($N = 239$)
Continuous covariates, mean (SD)			
Age (years)	62.9 (10.4)	65.4 (9.72)	64.4 (10.1)
Body weight (kg)	81.0 (19.8)	75.5 (14.6)	77.8 (17.1)
Serum creatinine (μmol/L)	97.7 (50.0)	84.9 (25.9)	90.2 (38.2)
Creatinine clearance (mL/min)[a]	80.6 (29.7)	82.4 (30.7)	81.7 (30.2)
Estimated glomerular filtration rate (mL/min/1.73 m^2)[b]	70.1 (22.2)	75.4 (22.5)	73.2 (22.5)
Albumin (g/L)	35.8 (5.68)	39.2 (6.35)	37.8 (6.30)
Aspartate transaminase (U/L)	32.9 (34.1)	22.5 (11.1)	26.8 (24.0)
Alanine transaminase (U/L)	27.9 (22.4)	21.1 (12.5)	23.9 (17.6)
Alkaline phosphatase (U/L)	67.8 (35.0)	70.9 (38.8)	69.6 (37.2)
Total bilirubin (μmol/L)	9.21 (5.28)	8.68 (4.91)	8.90 (5.06)
Total protein (g/L)	79.7 (18.9)	82.4 (15.3)	81.3 (16.9)
Baseline serum M-protein (g/L)	20.6 (19.2)	18.3 (16.2)	19.2 (17.5)
Categorical covariates, *n* (%)			
Sex			
Male	57 (57.6)	74 (52.9)	131 (54.8)
Female	42 (42.4)	66 (47.1)	108 (45.2)

TABLE 2 (Continued)

	EQUULEUS ($n = 99$)	APOLLO ($n = 140$)	Combined ($N = 239$)
Body weight category			
<65 kg	23 (23.2)	40 (28.6)	63 (26.4)
≥65 to <85 kg	38 (38.4)	64 (45.7)	102 (42.7)
≥85 kg	38 (38.4)	36 (25.7)	74 (31)
Extreme body weight			
<50 kg	3 (3.0)	1 (0.7)	4 (1.7)
≥120 kg	3 (3.0)	0	3 (1.3)
Age category			
≥18 to <65 years	51 (51.5)	58 (41.4)	109 (45.6)
≥65 to <75 years	40 (40.4)	58 (41.4)	98 (41.0)
≥75 years	8 (8.1)	24 (17.1)	32 (13.4)
Race			
White	77 (77.8)	124 (88.6)	201 (84.1)
Non-White	22 (22.2)	16 (11.4)	38 (15.9)
Renal function[c]			
Normal (≥90 mL/min)	35 (35.4)	47 (33.6)	82 (34.3)
Mild impairment (≥60 and <90 mL/min)	35 (35.4)	59 (42.1)	94 (39.3)
Moderate impairment (≥30 and <60 mL/min)	28 (28.3)	32 (22.9)	60 (25.1)
Severe impairment (≥15 and <30 mL/min)	1 (1.0)	2 (1.4)	3 (1.3)
Hepatic function			
Normal	76 (76.8)	127 (90.7)	203 (84.9)
Mild impairment	22 (22.2)	12 (8.6)	34 (14.2)
Moderate impairment	1 (1.0)	1 (0.7)	2 (0.8)
ECOG PS score			
0	27 (27.3)	86 (61.4)	113 (47.3)
1	60 (60.6)	49 (35)	109 (45.6)
2	12 (12.1)	5 (3.6)	17 (7.1)
Number of prior lines of therapy			
1	3 (3.0)	15 (10.7)	18 (7.5)
2 and 3	45 (45.5)	104 (74.3)	149 (62.3)
≥4	51 (51.5)	21 (15.0)	72 (30.1)
Type of myeloma (IgG *vs.* non-IgG)[d]			
IgG	60 (60.6)	72 (51.4)	132 (55.2)
Non-IgG	39 (39.4)	32 (22.9)	71 (29.7)
N missing (%)	0	36 (25.7)	36 (15.1)
PI/IMiD refractory status[e]			
None	0	20 (14.3)	20 (8.4)
PI only	8 (8.1)	5 (3.6)	13 (5.4)
IMiD only	21 (21.2)	30 (21.4)	51 (21.3)
Both PI and IMiD	70 (70.7)	85 (60.7)	155 (64.9)
ISS stage			
I	0	66 (47.1)	66 (27.6)
II	0	48 (34.3)	48 (20.1)
III	0	26 (18.6)	26 (10.9)
N missing (%)	99 (100)[f]	0	99 (41.4)

(Continues)

TABLE 2 (Continued)

	EQUULEUS ($n = 99$)	APOLLO ($n = 140$)	Combined ($N = 239$)
Anti-daratumumab antibodies[g]			
No	45 (45.5)	119 (85.0)	164 (68.6)
Yes	0	2 (1.4)	2 (0.8)
N missing (%)	54 (54.5)	19 (13.6)	73 (30.5)
Anti-rHuPH20 antibodies (baseline)[e]			
No	0	116 (82.9)	116 (48.5)
Yes	0	6 (4.3)	6 (2.5)
N missing (%)	99 (100)	18 (12.9)	117 (49.0)
Anti-rHuPH20 antibodies (treatment-emergent)[g]			
No	0	113 (80.7)	113 (47.3)
Yes	0	9 (6.4)	9 (3.8)
N missing (%)	99 (100)	18 (12.9)	117 (49.0)
Route of administration			
IV	99 (100)	3 (2.1)	102 (42.7)
SC	0	133 (95.0)	133 (55.6)
IV/SC	0	4 (2.9)	4 (1.7)

Abbreviations: CRT, serum creatinine; DSTP, baseline disease type; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; IgG, immunoglobulin G; IMiD, immunomodulatory drug; ISS, International Staging System; IV, intravenous; PI, proteasome inhibitor; PK, pharmacokinetic; PPK, population pharmacokinetics; rHuPH20, recombinant human hyaluronidase PH20; SC, subcutaneous; SD, standard deviation; TPMM, baseline myeloma type.

[a]Baseline creatinine clearance was calculated as follows: creatinine clearance = (weight in kg) × (140 − age in years)/72/(CRT/88.4) × (0.85 [if female]).

[b]Baseline eGFR was calculated as follows: eGFR (mL/min/1.73 m^2) = 175 × ([CRT/88.4]$^{-1.154}$) × (age$^{-0.203}$) × (0.742 if female) × (1.212 if African American) × (0.808 if Japanese).

[c]Renal function was calculated based on creatinine clearance.

[d]Baseline IgG myeloma is derived according to both TPMM and DSTP in APOLLO. If TPMM = IgG and DSTP = serum or serum and urine, baseline IgG myeloma is positive, otherwise it is negative. In EQUULEUS, baseline IgG myeloma is derived based only on TPMM.

[e]Patients refractory to a certain regimen are considered refractory to all drugs in such regimen.

[f]Data not available in clinical database.

[g]Only immunogenicity data from PK-evaluable patients included in the PPK analysis dataset are presented in this table.

2.3 | Exploratory PK analysis

Data exploration was performed via graphical or numerical summaries to explore the range of daratumumab concentrations and to facilitate outlier identification, examination of covariate correlations and comparison of PK following SC or IV administration of daratumumab in combination with Pd. Outliers were defined as aberrant observations, based on visual examination, that substantially deviated from the remaining observations within or across patients. Outliers ($n = 2$) and samples below the limit of quantitation ($n = 27$ [1.5%]) were excluded from the analysis datasets.

2.4 | Population PK modelling

2.4.1 | Model fitting

A previously developed PPK structural and covariate model for daratumumab IV/SC monotherapy was used as a starting point to fit the concentration–time data of daratumumab in patients with RRMM who received D-Pd combination therapy.[14] The covariate effect would be removed from this model if found to be not statistically significant based on their asymptotic 95% confidence interval (CI). Alternative structural models would be tested if the previously developed model did not describe the current data well.

The developed PPK model for IV/SC administration included a two-compartment structure with parallel linear and Michaelis–Menten nonlinear elimination pathways, as shown in Figure 1.[14] The absorption of the SC formulation was modelled with a first-order absorption process. The linear CL represents the nonspecific clearance for IgG, and the Michaelis–Menten elimination represents the saturable target-mediated clearance. The observed decrease in daratumumab clearance over time, which might be due to the treatment effect of daratumumab leading to a decrease in total target (CD38) number, was investigated using an empirical function $TDVM = V_{max} \cdot \exp(-K_{DES} \cdot t)$, in which *TDVM* represents the time-dependent maximum capacity of the saturable clearance and K_{DES} represents the first-order rate constant. This function describes the decrease of the V_{max} of the saturable CL process over time (t).

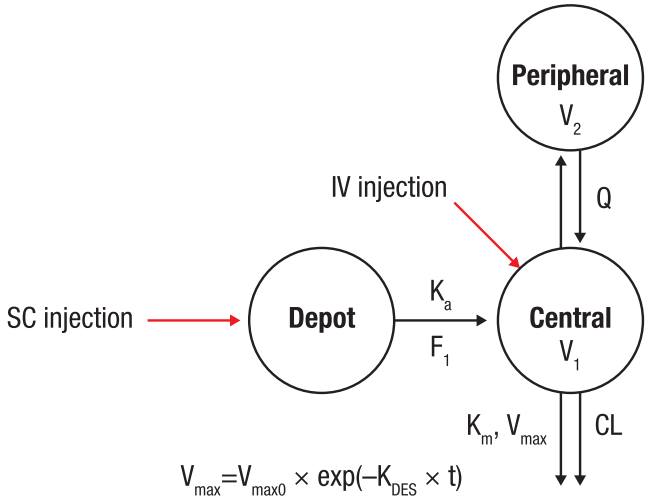

FIGURE 1 Michaelis–Menten pharmacokinetic model for daratumumab IV/SC. IV, intravenous; SC, subcutaneous; K_a, absorption rate constant; F_1, bioavailability; V_2, volume of distribution in the peripheral compartment; Q, intercompartmental clearance; V_1, volume of distribution in the central compartment; K_m, Michaelis-Menten constant; V_{max}, maximum velocity of the saturable clearance process, which decreases over time through a first-order rate (K_{DES}) from the initial maximum capacity V_{max0}; L, linear clearance; K_m.

The inter-patient variability in structural parameters was modelled with an exponential term to ensure positive values of individual parameters. An additive model on log-transformed concentrations was used to model residual variability.

2.4.2 | Covariate analysis

The relationship between physiological or pathological covariates and parameter estimates were explored (i.e., baseline continuation covariates: age, body weight, serum creatinine, creatinine clearance, estimated glomerular filtration rate, albumin, aspartate transaminase, alanine transaminase, alkaline phosphatase, total bilirubin, total protein, NK-cell, serum M-protein, kappa free light chain, lambda free light chain, free light chain, and lactate dehydrogenase; baseline categorical covariates: sex, race, renal and hepatic function, Eastern Cooperative Oncology Group [ECOG] performance status score, myeloma type [IgG *vs*. non-IgG], number of prior lines of therapy, proteasome inhibitor/immunomodulatory drug refractory status, and International Staging System [ISS] disease stage).

The covariate search was performed in two steps. The first step was to verify whether the previous covariate model applied to the current D-Pd population by testing whether the covariate effect parameter was equal to zero (using the asymptotic 95% CI), corresponding to no effect. The second step was to assess the need for an additional covariate search by inspecting plots of empirical Bayes estimates of random effects versus covariates. A covariate was integrated in the PPK model if two criteria were met: the empirical Bayes estimates of random effects-covariate relationship was statistically significant (i.e., $P < .05$) and the coefficient of determination (R^2) was >.15. The cut-off to define covariate clinical relevance on model-predicted PK exposures was 20%, as has been reported previously.[14]

2.4.3 | Model evaluation

Model evaluation was based on the objective function value (OFV) if models were nested (Akaike information criteria [AIC] otherwise), acceptable parameter precision and goodness-of-fit. Visual and/or numerical predictive checks (VPCs) were also used to assess model adequacy.

2.5 | PK simulations

2.5.1 | PK profile simulations

Simulations were performed using post-hoc PK parameters or typical PK parameters (for the clearances *vs*. time plot) from the final PK model to graphically compare: (1) D-Pd combination therapy *vs*. previous monotherapy; (2) daratumumab SC 1800 mg *vs*. daratumumab IV 16 mg/kg trough daratumumab concentrations, target saturation and clearance over time under the approved dose schedules.

2.5.2 | Model-predicted PK exposure under approved dosing regimen for subgroup analysis

Selected model-predicted PK exposure metrics were generated by simulations using post-hoc PK parameters following the approved (planned) dosing regimen for APOLLO and EQUULEUS patients to avoid any potential bias in the subgroup analysis that might be due to a difference in the received dose. These model-predicted exposure metrics were then compared using forest plots to evaluate the drug exposure in different subpopulations. For each covariate, two to three subgroups were defined based on covariate values and percentage change (mean and 95% CI) in exposure metrics between these subgroups was calculated. The reference subgroup was selected as the most relevant subgroup in the analysis population.

2.5.3 | Model-predicted PK exposure under actual dosing regimen for exposure-response analysis

Selected model-predicted PK exposure metrics were generated by simulations using post-hoc PK parameters following the actual dosing regimen for APOLLO patients receiving daratumumab. Exposure metrics included predicted peak (i.e., highest) concentration after first dose ($C_{peak,first}$), predicted C_{trough} after the first actual dose ($C_{trough,first}$), predicted maximum peak (i.e., highest) concentration over the entire treatment period ($C_{peak,max}$), predicted trough concentration at Cycle 3 Day 1 ($C_{trough,C3D1}$), and predicted maximum trough

concentration over the entire treatment period ($C_{trough,max}$). All exposure metrics were predicted during the period of treatment with daratumumab. As such, Cycle 3 Day 1 exposure was predicted for all patients still receiving daratumumab treatment at Cycle 3 Day 1; and $C_{peak,max}$ and $C_{trough,max}$ were predicted as the maximum metrics during the entire treatment time course. Temporary dose interruptions or delays during the on-treatment period were considered for the predictions. Additional details are provided in Supplementary Methods section in the Supporting Information.

2.6 | E-R analysis

The E-R analysis included data from all patients in APOLLO who received at least one dose of study drug(s) (for the D-Pd and Pd groups) and had at least one evaluable PK sample (for the D-Pd group). The relationship between model-predicted daratumumab exposure and progression-free survival (PFS) was evaluated graphically and analysed using Kaplan–Meier (using exposure quantiles groups) and Cox-proportional (using exposure as a continuous regressor) analyses. The three model-predicted PK exposure metrics used for the efficacy E-R analysis were $C_{peak,first}$, $C_{trough,first}$ and $C_{trough,max}$. No other covariates were investigated in the exposure–efficacy analysis due to the absence of relevant relationships identified in subgroup analyses of an earlier publication of the APOLLO study,[25] as well as other previous studies.[21]

The E-R analysis for safety was explored for selected TEAEs of clinical interest, including IRRs, neutropenia, anaemia, thrombocytopenia and infections. TEAE rates were computed for all grades and grade ≥3. The influence of body weight on TEAEs was also explored. Similar to the exposure–efficacy analysis, no additional covariates were investigated in the exposure–safety analysis. The two model-predicted PK exposure metrics used for the safety E-R analysis were $C_{peak,first}$ for IRRs (because the majority of IRRs occurred during the first infusion[23]) and $C_{peak,max}$ for all other TEAEs. These metrics had been used for the selected adverse events in previous publications of other daratumumab indications.[14,15] All model-predicted exposure metrics for the E-R analysis were derived using each patient's actual dosing information.

2.7 | Modelling software

For the PPK model, data were analysed using NONMEM® version 7.3.0 (ICON Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation (FOCE) method was used for continuous dependent variables. The INTERACTION option was used when the residual error model was dependent on predicted values (e.g., proportional error). PsN Version 3.4.2 was used to execute NONMEM analyses. Exploratory analysis, diagnostic graphics, post-processing of NONMEM analysis results and the E-R analysis were carried out using R Project for Statistical Computing, Version 3.4.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[26]

3 | RESULTS

3.1 | PPK analysis

The final PPK dataset contained 1146 daratumumab PK samples (473 SC samples and 673 IV samples) from 239 PK-evaluable patients from the D-Pd cohort of APOLLO ($n = 140$) and the D-Pd cohort of EQUULEUS ($n = 99$). In APOLLO, 133 patients received daratumumab SC 1800 mg, four received daratumumab IV 16 mg/kg and then switched to SC 1800 mg, and three received daratumumab IV 16 mg/kg only. All EQUULEUS patients received daratumumab IV 16 mg/kg. Patient demographic and baseline clinical characteristics are described in Table 2.

An exploratory analysis showed that daratumumab serum concentration–time profiles following D-Pd combination therapy were in similar ranges across the APOLLO and EQUULEUS studies and across both SC and IV routes of administration (Figure S1).

3.1.1 | Final model

PK of daratumumab could be adequately described by a two-compartment PPK model with a first-order absorption rate and parallel linear and nonlinear Michaelis–Menten elimination pathways (Figure 1). Based on these results, no other structural models were tested.

Body weight, albumin concentration and type of myeloma (IgG *vs.* non-IgG) were identified as statistically significant covariates on linear clearance, while body weight and sex were identified as statistically significant covariates on volume of distribution in the central compartment. No other covariate was found to influence model PK parameters, as shown by the absence of trend in the plot of empirical Bayes estimates of random effects versus covariates. This was also consistent with the previous PPK IV/SC covariate model for monotherapy and other combination therapies.

The parameter estimates of the final model are provided in Table 3. Daratumumab concentrations rose slowly after SC administration (first-order absorption rate of 0.0120 h^{-1} [0.288 day^{-1}]). The estimated CL (0.00432 L/h [0.104 L/day]) was very close to the reported clearance of nonspecific endogenous IgG in the literature,[27] and the volume of distribution of the central compartment (4.36 L) was close to plasma volume; both parameters were related to body weight, as expected for mAbs. The model-derived geometric mean (coefficient of variation [CV%]) half-life associated with the linear elimination was 19.7 days (15.3%) based on post-hoc PK estimates.

TABLE 3 Parameter estimates of the daratumumab PPK model based on combined SC and IV data following D-Pd combination therapy

Parameter, unit	Description	Estimate	95% CI	RSE on estimate (%)	IIV (% CV)	RSE on IIV (%)
CL (L/h)	Linear clearance	0.00432	(0.00351, 0.00513)	9.51	43.5	8.65
ALB on *CL*[a]	Effect of serum albumin concentration on linear clearance	−0.665	(−1.13, −0.199)	35.8	–	–
WT on *CL*[a]	Effect of body weight on linear clearance	0.832	(0.483, 1.18)	21.4	–	–
TPMC on *CL*[a]	Effect of type of myeloma (IgG *vs.* non-IgG) on linear clearance	0.833	(0.517, 1.15)	19.3	–	–
V_1 (L)	Volume of distribution in the central compartment	4.36	(3.86, 4.86)	5.87	28.0	10.8
WT on V_1[b]	Effect of body weight on volume of distribution in the central compartment	0.562	(0.25, 0.874)	28.3	–	–
SEX on V_1[b]	Effect of sex (female *vs.* male) on volume of distribution in the central compartment	−0.168	(−0.28, −0.0563)	33.9	–	–
V_2 (L)	Volume of distribution in the peripheral compartment	2.80	(2.00, 3.60)	14.6	–	–
Q (L/h)	Intercompartmental clearance	0.00814	(0.00483, 0.0115)	20.8	–	–
V_{max} (mg/h)	Maximum velocity of the saturable clearance process	1.47	(1.09, 1.85)	13.1	59.6	13.4
K_{DES} (1/h)	First-order rate for decrease of maximum velocity of the saturable clearance process over time	0.000282	(0.000154, 0.000410)	23.2	75.3	20.2
K_m (μg/mL)	Michaelis–Menten constant	3.81	(1.20, 6.42)	34.9	–	–
Ka (1/h)	First-order absorption rate	0.0120	(0.00967, 0.0143)	9.9	55.4	12.2
F_1	Bioavailability	0.689 (FIX)	–	–	–	–
ADD ERR (%CV)	Additive error term on the log-scale	27.7	(26.7, 28.7)	1.8	–	–

Note: Objective function value = −780.8. Condition number = 41.7. RSE% for IIV and ADD ERR are reported on the approximate standard deviation scale (standard error/variance estimate)/2. CV% for IIV and ADD ERR are computed as sqrt(ω2) and sqrt (σ2), respectively. 95% CIs are calculated based on standard error from the covariance matrix assuming PK parameters are normally distributed.

Abbreviations: CI, confidence interval; CV, coefficient of variation; D-Pd, daratumumab SC or IV in combination with pomalidomide and dexamethasone; FIX, not estimated; IgG, immunoglobulin G; IIV, interindividual variability; IV, intravenous; PK, pharmacokinetic; PPK, population pharmacokinetics; RSE, relative standard error; SC, subcutaneous; TPMC, type of myeloma (IgG vs. non-IgG); TVCL, typical value of clearance; TVV, typical value of volume of distribution.

[a] $TVCL = 0.00432 \cdot \left(\frac{WT}{76}\right)^{0.832} \cdot \left(\frac{ALB}{38}\right)^{-0.665} \cdot TPMC_{CL}$, where $TPMC_{CL}$ is a shift factor of 1 for non-IgG multiple myeloma patients and 1 + 0.833 = 1.833 for IgG multiple myeloma patients.

[b] $TVV1 = 4.36 \cdot \left(\frac{WT}{76}\right)^{0.562} \cdot SEX_{V1}$, where SEX_{V1} is a shift factor of 1 for male and 1 − 0.168 = 0.832 for female.

3.1.2 | Model evaluation

Goodness-of-fit plots for the final PPK model are provided in Figure S2. The plots of individual predictions *vs.* observations showed no marked deviation from the identity line. The plots of conditional weighted residuals (CWRES) *vs.* population predictions and *vs.* time showed no marked deviation from the zero line and homogeneous variation, suggesting an adequate fit of the final PPK model to the data. There was a slight overprediction for low nontherapeutic concentrations and at early time points after first dose, which might be because the model did not account for the fraction of dose that is bound to the receptor after administration. However, for the most part, |CWRES| was within 5. Additionally, histograms and plots of empirical Bayes estimates of random effects showed no marked deviation from the normal distribution.

The performance of the final PPK model was evaluated using VPC. As shown in Figure 2, the final PPK model provided a good description of the data. Additional VPCs for APOLLO stratified by body weight or pre-dose/post-dose further demonstrated the ability of the final PPK model to well describe the APOLLO data (data not shown).

3.2 | PK simulations

3.2.1 | Comparison of D-Pd combination therapy and historical daratumumab monotherapy

The model-predicted PK profiles of daratumumab were considered comparable between D-Pd combination and historical daratumumab monotherapy. Simulated $C_{trough,C3D1}$ were similar, with median concentration 23% higher with D-Pd combination and significant overlap in the simulated concentration ranges as shown in Figure S3. CL, volumes of distribution, and absorption rate parameter estimates were similar to the previously reported estimates for monotherapy (differences <30%). The model-derived geometric mean (CV%)

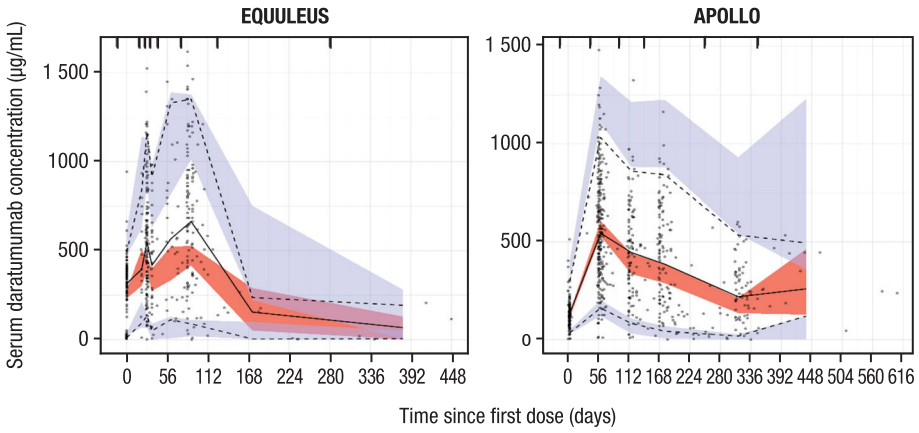

FIGURE 2 Visual predictive check for the final population pharmacokinetic model stratified by study. Black circles represent observations. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles simulated by the model, respectively.

half-life associated with linear elimination was 19.7 days (15.3%), comparable to the estimated half-life of 20.4 days (22.4%) derived from the previously reported estimates for monotherapy. These similarities in daratumumab PK between the current study and historical monotherapy confirmed that the combination therapy with Pd had no influence on daratumumab PK in patients with RRMM.

3.2.2 | Model-predicted PK profile, target saturation profile and clearance profile under the approved dosing regimen

The simulated PK profiles (median and 90% prediction interval) for daratumumab SC 1800 mg and daratumumab IV 16 mg/kg administered per the approved dosing regimen provided similar model-predicted exposure in patients with RRMM (Figure 3A). Simulated daratumumab concentrations appear stable during every 2-week (Q2W) dosing from Week 16 (from first dose) until a change in frequency of dosing to every 4-week (Q4W) dosing at Week 24. Apparent steady state appeared to be reached approximately 5 months into the Q4W dose schedule. The model-predicted daratumumab SC 1800 mg dose resulted in smaller peak-to-trough fluctuations, lower C_{max} and higher C_{trough} throughout the approved dose schedule compared with daratumumab IV 16 mg/kg. The median peak-to-trough ratio during the last week of weekly dosing (Week 8) for daratumumab SC 1800 mg was 1.07 (90% prediction interval: 1.01–1.26).

Model-predicted target saturation, calculated based on the simulated concentrations and the estimated Michaelis–Menten constant (K_m), was maintained over 95% during all phases (once weekly [QW], Q2W, Q4W) of the approved daratumumab dose schedules for all patients enrolled in the PPK analysis dataset, regardless of body weight (Figure S4).

The dynamics of the simulated typical clearance profiles following the approved daratumumab dosing regimen of SC 1800 mg and IV 16 mg/kg are shown in Figure 3B. The total clearance decreased over time and approached the nonspecific CL after about 16 weeks. This is likely due to the decrease of the tumour burden or target induced by daratumumab. The model-predicted clearance profiles following the administration of daratumumab SC are similar to those following daratumumab IV, with the only difference during the first administration. This was because, after the first IV administration, daratumumab concentration could reach a high level within a short infusion time and receptors became saturated. After the first SC administration, model-predicted daratumumab concentration gradually increased due to the slower absorption of daratumumab into systemic circulation, leading to slow receptor saturation and higher clearance than IV at the beginning of first administration.

3.2.3 | Comparison of model-predicted daratumumab exposure in subpopulations

The forest plot showed that the simulated daratumumab $C_{trough,C3D1}$ (prior to the first dose of the Q2W dose schedule) was highly consistent across different subgroups (Figure 4). The largest differences were observed for the statistically significant covariates identified on CL in the PPK modelling (i.e., body weight, albumin concentration and type of myeloma), but none of the investigated covariates were clinically relevant, with a geometric mean percentage change in $C_{trough,C3D1}$ of <20% compared with the reference group.

3.3 | Exploratory E-R analysis for efficacy

The final E-R dataset, used for both efficacy and safety E-R analyses, contained data from 290 patients from APOLLO (D-Pd cohort, $n = 140$; Pd cohort, $n = 150$). A summary of baseline covariates for the E-R population is available in Table S1.

Efficacy data from APOLLO showed robust activity of daratumumab SC 1800 mg in combination with Pd, with statistically significant improvements in PFS compared with the control group and consistent clinical benefit across clinically important subgroups (e.g., ISS stage, ECOG status). In particular, all body weight subgroups showed clinical benefit of D-Pd *vs*. Pd. The E-R analysis on efficacy data suggests that a marked daratumumab effect on PFS has been attained for the majority (75%) of patients with model-predicted exposures greater

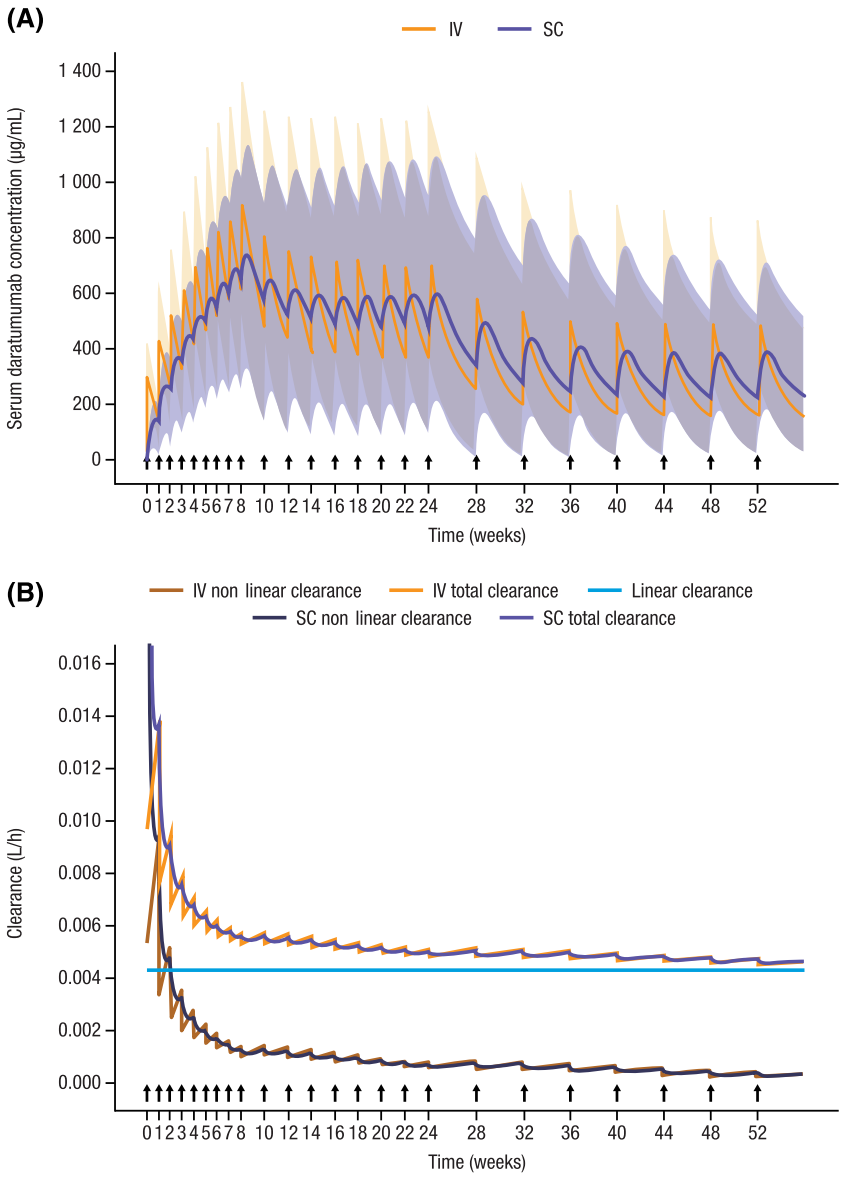

FIGURE 3 (A) Simulated median pharmacokinetic profile and 90% prediction interval of daratumumab after daratumumab SC 1800 mg or daratumumab IV 16 mg/kg administration per the approved dose schedule for D-Pd combination therapy. (B) Simulated typical total, linear and nonlinear clearance *vs.* time profiles after daratumumab SC 1800 mg or daratumumab IV 16 mg/kg administration per the approved dose schedule for D-Pd combination therapy. Black arrows represent dose events. The shaded orange and blue areas represent the 90% prediction interval of daratumumab PK (using post-hoc PK parameters from the $n = 133$ patients for SC from APOLLO, $n = 106$ patients for IV [99 from EQUULEUS and 7 from APOLLO]). Note: Approved dose schedule consisted of QW for 8 weeks (eight doses), Q2W for 16 weeks (eight doses) and Q4W thereafter (eight doses). SC, subcutaneous; IV, intravenous; D-Pd, daratumumab SC or IV in combination with pomalidomide and dexamethasone; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

than the first exposure quartile (Q1) at the studied 1800 mg SC dose regardless of exposure metric investigated (Figure 5). Although there was no apparent PFS improvement for patients in Q1 in the D-Pd group compared to the Pd group, the lower model-predicted exposure in D-Pd Q1 was not related to body weight (mean [standard deviation] body weight was 79.7 kg [15.7] in D-Pd Q1, and 81.4 kg [12.6] in the D-Pd second quartile [Q2] for C_{trough} after the first administration). The E-R analysis using model-predicted exposure as a continuous regressor led to similar conclusions, with increasing exposure leading to improved PFS (hazard ratios [95% CIs] of 0.48 [0.35–0.64], 0.65 [0.52–0.81] and 0.53 [0.42–0.67]) for median values of first peak, first trough and maximum trough, respectively (Figure 6). Lastly, a case-matching E-R analysis was performed to investigate whether an imbalance in covariates could explain the lack of apparent improvement in PFS in D-Pd-Q1 patients, even if treatment effect had previously been found to be consistent across clinically relevant subpopulations.[14,21] Investigated covariates were the same as in the clinical subgroup analysis (i.e., age, sex, race, ISS stage, number of prior lines of therapy, type of myeloma, cytogenetic risk, renal and hepatic function, and refractory status to lenalidomide). In this additional analysis, the PFS of D-Pd-Q1 patients was compared to the PFS of a subset of Pd patients selected to match the covariate distribution of the D-Pd-Q1 patients for selected covariates. Results of the case-matched E-R analysis were similar to those of the unmatched E-R analysis, concluding that an imbalance in covariates could not explain the lack of apparent improvement in PFS in D-Pd-Q1 patients.

3.4 | Exploratory E-R analysis for safety

There was no apparent increase in TEAE rates with increasing model-predicted exposure ($C_{peak,first}$ or $C_{peak,max}$) for IRRs, thrombocytopenia, anaemia, neutropenia and infections (all grades and grades ≥3) within the studied drug concentration range in APOLLO (Table 4). A trend of

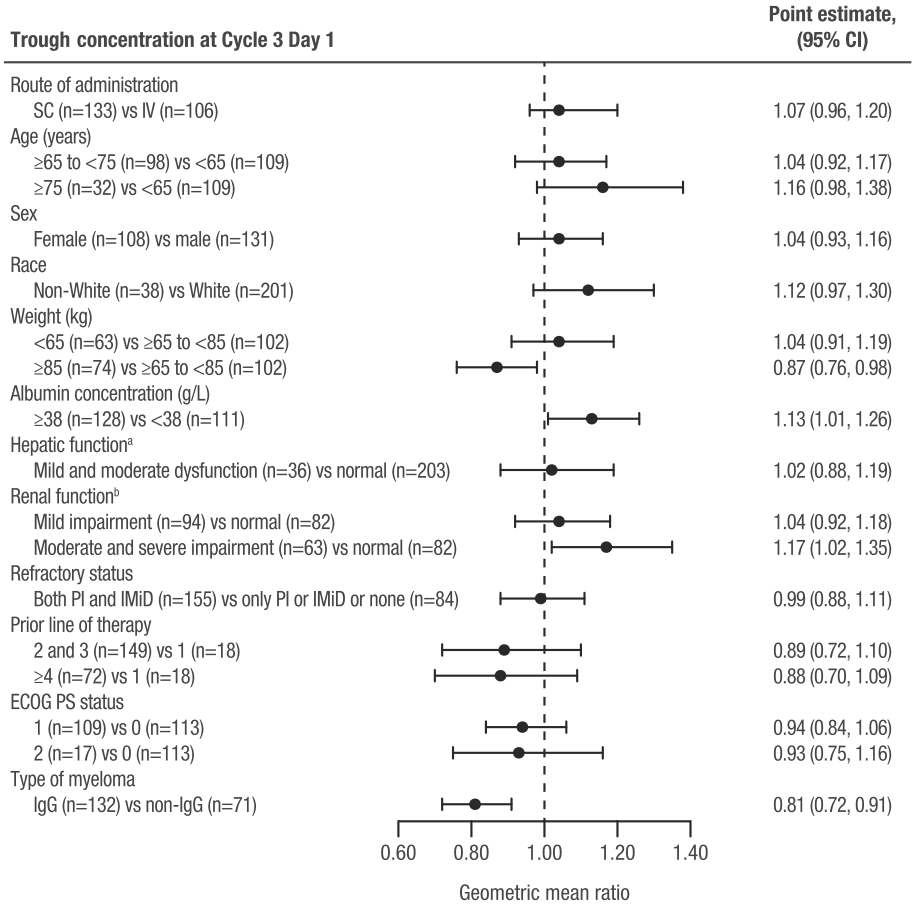

FIGURE 4 Forest plot of subgroup analyses on percentage change and 95% CI relative to reference value for simulated trough concentration at Cycle 3 Day 1 per the approved dose schedule for D-Pd combination therapy. Solid black points represent percentage change of geometric mean and short horizontal bars represent 95% CI. Dashed line represents reference value of 0. Numbers represent percentage of change and the associated CI. Analyses assumed that all PK-evaluable patients ($n = 239$) in the APOLLO and EQUULEUS D-Pd cohorts received 16 mg/kg weekly for 8 weeks (eight doses), Q2W for 16 weeks (eight doses), and then Q4W thereafter. The four patients first administered daratumumab IV 16 mg/kg and then switched to SC 1800 mg were assumed to have received IV administration throughout. The number of patients in the reference group for each covariate was as follows: route of administration IV ($n = 106$ [7 from APOLLO and 99 from EQUULEUS]); age <65 years ($n = 109$); male ($n = 131$); White ($n = 201$); body weight 65 to 85 kg ($n = 102$); albumin concentration ≥38 g/L ($n = 111$); normal hepatic function ($n = 203$); normal renal function ($n = 82$); refractory status only PI or IMiD or none ($n = 84$); one prior line of therapy ($n = 18$); ECOG PS 0 ($n = 113$); non-IgG myeloma ($n = 71$). The type of myeloma was missing for 36 patients. Two patients had moderate hepatic impairment and were combined with patients with mild hepatic impairment. Three patients had severe renal impairment and were combined with patients with moderate renal impairment. Patients refractory to a certain regimen were considered refractory to all drugs in such regimen. [a]Normal hepatic function was defined as total bilirubin and AST ≤ ULN; mild hepatic impairment was defined as total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5 × ULN; moderate hepatic impairment was defined 1.5 × ULN < total bilirubin ≤ 3 × ULN. [b]Calculated via creatinine clearance (normal, ≥90 mL/min; mild impairment, ≥60 to <90 mL/min; moderate impairment, ≥30 to <60 mL/min; severe impairment, <30 mL/min). CI, confidence interval; D-Pd, daratumumab SC or IV in combination with pomalidomide and dexamethasone; SC, subcutaneous; IV, intravenous; PI, proteasome inhibitor; IMiD, immunomodulatory drug; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG, immunoglobulin G; PK, pharmacokinetics; Q2W, every 2 weeks; Q4W, every 4 weeks; AST, aspartate aminotransferase; ULN, upper limit of normal.

inverse relationship between the event rates of neutropenia, anaemia and thrombocytopenia and $C_{peak,max}$ was observed, likely because patients with TEAEs tended to have dose interruption or delays leading to lower concentrations at $C_{peak,max}$ despite having potentially higher exposures prior to treatment interruptions. No increase in rates of the TEAEs investigated in this E-R analysis has been observed in the clinical statistical analysis with the lower body weight subgroup, except for anaemia. However, the higher anaemia rate with low body weight was likely not related to an increase in exposure as, in the E-R analysis, increased model-predicted exposure was associated with lower anaemia rates.

4 | DISCUSSION

The current study provides a characterization of the PK and E-R relationships of daratumumab SC or IV for a new indication, that is, for the treatment of RRMM in combination with Pd in patients who have

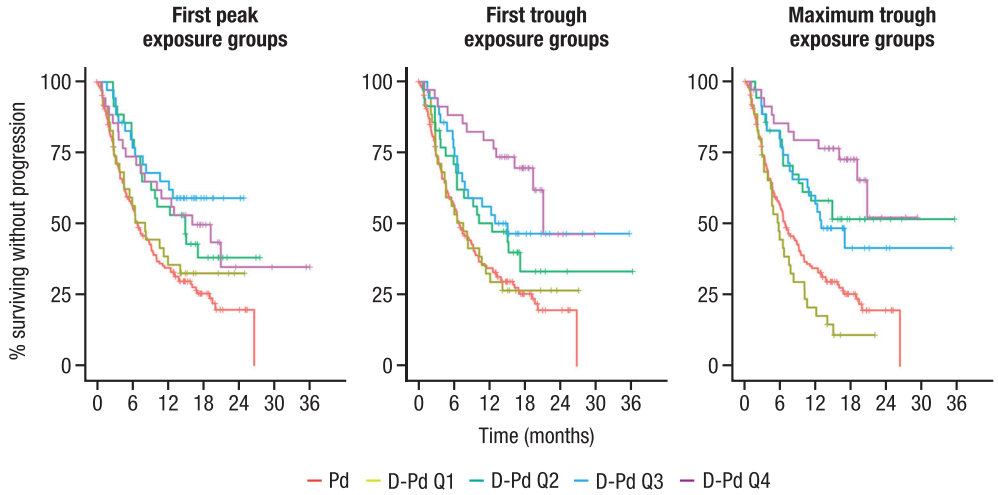

FIGURE 5 Kaplan–Meier curves of PFS by daratumumab exposure subgroups in combination with Pd in APOLLO. PFS, progression-free survival; Pd, pomalidomide and dexamethasone; D-Pd, daratumumab SC or IV in combination with pomalidomide and dexamethasone; Q1, first quartile of model-predicted daratumumab exposure; Q2, second quartile of model-predicted daratumumab exposure; Q3, third quartile of model-predicted daratumumab exposure; Q4, fourth quartile of model-predicted daratumumab exposure; SC, subcutaneous; IV, intravenous; $C_{peak,first}$, predicted peak concentration after first dose; $C_{trough,first}$, predicted trough concentration after first dose; $C_{trough,max}$, predicted overall maximum trough concentration. The model-predicted quartiles for $C_{peak,first}$ were: Q1 (≤121 μg/mL), Q2 (>121 to ≤151 μg/mL), Q3 (>151 to ≤185 μg/mL) and Q4 (>185 to ≤374 μg/mL). The quartiles for $C_{trough,first}$ were: Q1 (≤109 μg/mL), Q2 (>109 to ≤135 μg/mL), Q3 (>135 to ≤161 μg/mL) and Q4 (>161 to ≤239 μg/mL). The quartiles for $C_{trough,max}$ were: Q1 (≤398 μg/mL), Q2 (>398 to ≤544 μg/mL), Q3 (>544 to ≤722 μg/mL) and Q4 (>722 to ≤1261 μg/mL).

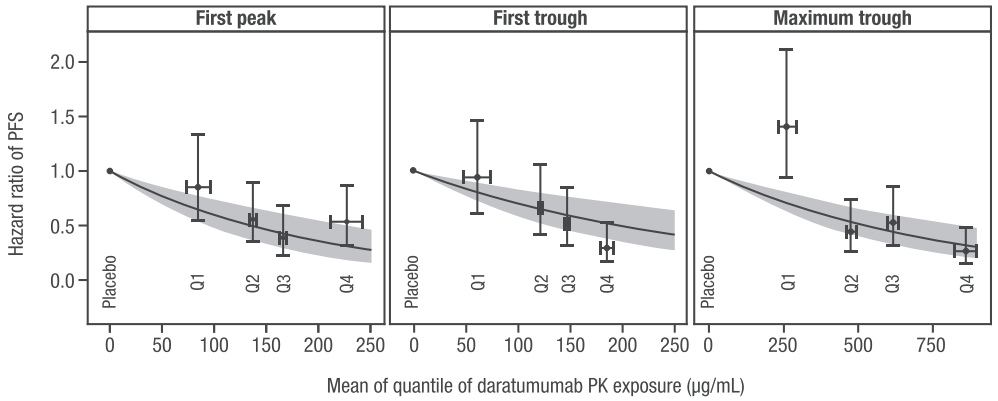

FIGURE 6 PFS hazard ratio *vs.* model-predicted daratumumab exposures in combination with Pd in APOLLO. Points and vertical error bars correspond to hazard ratios and their 95% CIs estimated by Kaplan–Meier analysis for each exposure group. Horizontal error bars represent the 95% CIs of the mean concentration of the model-predicted PK exposure quantiles. The line and shaded area represent the hazard ratios and associated 95% CIs estimated from a Cox-proportional hazard model using model-predicted PK exposure as a continuous regressor. PFS, progression-free survival; Pd, pomalidomide and dexamethasone; Q1, first quantile of model-predicted daratumumab exposure; Q2, second quantile of model-predicted daratumumab exposure; Q3, third quantile of model-predicted daratumumab exposure; Q4, fourth quantile of model-predicted daratumumab exposure; PK, pharmacokinetic; CI, confidence interval.

received ≥2 prior therapies including lenalidomide and a proteasome inhibitor.

The observed concentration–time data of daratumumab after SC administration were well described by a two-compartment PPK model with first-order absorption and parallel linear and nonlinear elimination pathways. This was consistent with the previous daratumumab IV/SC PPK model for monotherapy and other combination therapies and showed that Pd did not impact daratumumab PK.[14,15] The change in nonlinear clearance over time was described as a function of time in the study, as previously done for daratumumab studies[28] and other compounds such as nivolumab.[29] The time-dependency was not sensitive to the limited treatment interruptions or discontinuations present in our data (median relative dose intensity of SC daratumumab, 94%; $n = 33$ post-treatment concentrations out of 1146 PK samples). Moving towards a more physiologic, mechanistic modelling of the changes in clearance to reflect target receptor and/or biomarker dynamics

TABLE 4 Comparison of TEAE rates across daratumumab exposure subgroups for D-Pd combination therapy in APOLLO

TEAE	Pd % (95% CI) $n = 150$	D-Pd exposure quartiles[a], % (95% CI) Q1 $n = 35$	Q2 $n = 35$	Q3 $n = 35$	Q4 $n = 35$
Neutropenia					
Any grade	53.3 (45.3, 61.2)	82.9 (68.3, 92.8)	77.1 (61.6, 88.8)	71.4 (55.3, 84.5)	71.4 (55.3, 84.5)
Grade ≥3	50.7 (42.7, 58.6)	74.3 (58.4, 86.7)	74.3 (58.4, 86.7)	71.4 (55.3, 84.5)	71.4 (55.3, 84.5)
Infections					
Any grade	55.3 (47.3, 63.1)	74.3 (58.4, 86.7)	74.3 (58.4, 86.7)	71.4 (55.3, 84.5)	71.4 (55.3, 84.5)
Grade ≥3	23.3 (17.1, 30.5)	42.9 (27.4, 59.3)	31.4 (17.7, 47.7)	25.7 (13.3, 41.6)	20.0 (9.1, 35.1)
Anaemia					
Any grade	44.7 (36.9, 52.7)	48.6 (32.6, 64.8)	42.9 (27.4, 59.3)	28.6 (15.5, 44.7)	25.7 (13.3, 41.6)
Grade ≥3	21.3 (15.3, 28.3)	34.3 (20.1, 50.7)	17.1 (7.2, 31.7)	5.7 (1.0, 16.6)	8.6 (2.2, 20.7)
Thrombocytopenia					
Any grade	33.3 (26.1, 41.1)	42.9 (27.4, 59.3)	37.1 (22.5, 53.6)	22.9 (11.2, 38.4)	20.0 (9.1, 35.1)
Grade ≥3	18.0 (12.4, 24.7)	31.4 (17.7, 47.7)	25.7 (13.3, 41.6)	5.7 (1.0, 16.6)	8.6 (2.2, 20.7)
IRRs[b]					
Any grade	0	8.6 (2.2, 20.7)	5.7 (1.0, 16.6)	2.9 (0.2, 12.0)	5.7 (1.0, 16.6)
Grade ≥3	0	0	0	0	0

Abbreviations: CI, confidence interval; $C_{peak,max}$, predicted maximum peak concentration; $C_{peak,first}$, predicted peak concentration after first dose; D-Pd, daratumumab SC or IV in combination with pomalidomide and dexamethasone; IRR, infusion-related reaction; n, maximum number of patients with data; Pd, pomalidomide and dexamethasone; TEAE, treatment-emergent adverse event; Q1, first quartile of daratumumab exposure; Q2, second quartile of daratumumab exposure; Q3, third quartile of daratumumab exposure; Q4, fourth quartile of daratumumab exposure.

[a]The quartiles for $C_{peak,max}$ were: Q1 (≤491 μg/mL), Q2 (>491 to ≤651 μg/mL), Q3 (>651 to ≤839 μg/mL), and Q4 (>839 to ≤1440 μg/mL). The quartiles for $C_{peak,first}$ were: Q1 (≤121 μg/mL), Q2 (>121 to ≤151 μg/mL), Q3 (>151 to ≤185 μg/mL), and Q4 (>185 to ≤374 μg/mL).

[b]$C_{peak,max}$ was used as the exposure measure for analyses on all adverse events except IRRs, where $C_{peak,first}$ was used.

(e.g., of tumour burden) would likely improve the model's predictive properties across indications. Despite having both IV and SC data, bioavailability (F_1) of the SC formulation was fixed, as estimation of F_1 in the complex PPK model was difficult based on data in D-Pd patients with sparse sampling (only troughs and few peak levels) that cannot easily distinguish absorption from elimination processes. Therefore, part of the PPK model was fixed to allow meaningful estimation of the parameters of most interest, in particular clearance parameters. The selection of the parameter(s) to be fixed was based on (1) the confidence in the accuracy of these parameters and (2) parsimony (i.e., fixing as few parameters as possible to enable stable model fit). Based on these criteria, F_1 was chosen as the fixed parameter. The fixed bioavailability of 0.689 was from the previous IV/SC PPK model,[14] and the confidence in its accuracy was high, as the data were rich (both in terms of number of patients, samples and sampling density) and there was minimal risk of bias in the estimation of F_1 through IV and SC profiles arising from randomized patients in a single study.

The baseline covariates body weight, albumin concentration, type of myeloma and sex were identified as statistically significant in the final PPK model. The effect of serum albumin on CL is likely because the neonatal Fc receptor (FcRn), which protects IgG or IgG-based mAbs from degradation, also binds to and protects albumin from intracellular catabolism. A higher albumin concentration could indicate a higher number of FcRns, which in turn may also increase the protection of daratumumab from nonspecific elimination. However, the subgroup analysis of $C_{trough,C3D1}$ showed that body weight, albumin concentration and type of myeloma were unlikely to be clinically relevant, with a difference of <20% on $C_{trough,C3D1}$. The subgroup analysis led to similar conclusions as previous analyses based on $C_{trough,max}$ of daratumumab IV and SC data, which also concluded that exposure differences between covariate subgroups were mostly <25%.[14,15,21] Only albumin and type of myeloma showed effects exceeding 25% in previous IV analyses,[15,21] which are likely linked to the study-protocol-based change in albumin cut-off (38 g/L in the current analysis *vs.* 35 g/L earlier) and between-study variability for type of myeloma (previous estimates ranging from −20% to −50% for IgG *vs.* non-IgG myeloma, compared with −19% in the current analysis). The present analysis thus shows the lack of relevant influence of any covariates on daratumumab PK in patients with RRMM treated with Pd and, therefore, no dose adjustment is recommended based on any of these factors. Immunogenicity response was not evaluated as a covariate in the PPK model due to the low number of patients developing antibodies to daratumumab or rHuPH20 (Table 2).

The APOLLO trial showed that the combination of SC daratumumab with Pd significantly improved median PFS versus Pd, with a median PFS of 12.4 months (95% CI, 8.3–19.3) in the D-Pd group and 6.9 months (95% CI, 5.5–9.3) in the Pd group.[25] The additional efficacy E-R analyses presented here supported improved PFS for

patients in the D-Pd group compared to the Pd group. The E-R analysis on efficacy data suggests that a marked daratumumab effect on PFS has been attained for 75% of participants at the studied 1800 mg SC dose regardless of exposure metric investigated, with statistically significant HR for increases in median first peak, first trough and maximum trough values.

A confounding effect may be present in the E-R analysis due to the time-varying clearance as a result of disease status improvement following treatment (i.e., clearance decreases as disease status improves).[29] This has been previously hypothesized for patients with MM where daratumumab IV was administered in combination with various background therapies, as well as for other mAbs such as nivolumab and trastuzumab.[29,30]

Patients with less improvement of disease tend to have lower exposures due to higher clearance, which may hamper the interpretation of the E-R relationship. To address this potential bias, early exposure metrics were used for this analysis. The absence of any association between exposure quantiles and time to censoring (all *P*-values >.05) evidenced the absence of informative missingness, and thus supports that the E-R analysis is not biased by imbalances in censoring. In the future, more advanced E-R analyses may be considered, in particular jointly analysing exposure and response, and/or other potential biomarkers.[31,32]

In the safety E-R analysis, the most commonly experienced TEAEs were neutropenia and infections, present for >70% of patients receiving D-Pd (*vs*. >50% in patients receiving Pd). In both groups, neutropenia was typically severe (mostly grade ≥3), whereas infection grades were more evenly spread. All-grade anaemia and thrombocytopenia were also common (>20%) for both the D-Pd and Pd groups. There was no apparent increase in the rate of any TEAE of interest with increasing PK exposure, indicating an acceptable safety profile across the studied body weight and concentration range. Overall, the safety profile was similar to that previously observed for monotherapy and other combinations.[23] Due to the limited trends in these data and the absence of weight-dependency of TEAEs identified from previous SC data, more complex safety E-R models (such as time-to-event modelling, which could alleviate potential confounding of treatment interruptions) were not investigated here.

Some general limitations common to PPK analyses apply to this study. Despite the large number of patients and samples from multiple trials of patients with RRMM, the study designs, daratumumab dosing regimens, inclusion criteria and PK sampling schedules of the included trials differed slightly. However, the PK data are consistent with previous reports with daratumumab and support the approved daratumumab SC dose of 1800 mg.

5 | CONCLUSION

The PPK and E-R analyses support the selected daratumumab SC 1800 mg with rHuPH20 co-formulation dosing regimen in combination with Pd for the treatment of patients with RRMM. Overall, none of the investigated factors had clinically relevant effects on daratumumab PK. Therefore, no dose adjustment is recommended based on these factors for the D-Pd SC combination.

ACKNOWLEDGEMENTS

The authors wish to thank the patients who participated in the clinical trials and the investigators and their staff at the clinical study sites for their valuable contribution. The study was supported by the European Myeloma Network (EMN) and Janssen Research & Development, LLC. Medical writing support was provided by Austin Horton, PhD, of Lumanity Communications Inc., and was funded by Janssen Global Services, LLC.

COMPETING INTERESTS

A.D., X.L., M.L., I.N., T.K. R.C., H.A., J.J.P.R., H.Z., Y.S. and Y.X. were employees of Janssen Research & Development, LLC, Pharmaceutical Companies of Johnson & Johnson, at the time of the study. M. A.D. has received honoraria from Amgen, BeiGene, BMS, Janssen and Takeda. E.T. has received research funding from Amgen, Celgene, Genesis, GSK, Janssen, Sanofi and Takeda; and has received honoraria from Amgen, BMS, Celgene, Genesis, GSK, Janssen, Novartis, Sanofi and Takeda. P.S. has received research funding from Amgen, Celgene, Janssen, Karyopharm, SkylineDx and Takeda; and has received honoraria from and served on advisory boards for Amgen, BMS, Celgene, Janssen, Karyopharm, SkylineDx and Takeda.

CONTRIBUTORS

All authors developed the manuscript, provided a full review and approval of the final version of the article, and are fully responsible for all content and accuracy of the data.

DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Research & Development, LLC, 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 the Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

ORCID

Anne-Gaelle Dosne https://orcid.org/0000-0002-6937-0910

REFERENCES

1. Hassan H, Szalat R. Genetic predictors of mortality in patients with multiple myeloma. *Appl Clin Genet*. 2021;14:241-254. doi:10.2147/TACG.S262866
2. Leow CC, Low MSY. Targeted therapies for multiple myeloma. *J Pers Med*. 2021;11(5):334. doi:10.3390/jpm11050334
3. Stankovikj S, Martinova K. Acute complications in multiple myeloma. *Sanamed*. 2017;12(2):115-120.
4. Sonneveld P, Broijl A. Treatment of relapsed and refractory multiple myeloma. *Haematologica*. 2016;101(4):396-406. doi:10.3324/haematol.2015.129189
5. de Weers M, Tai YT, van der Veer MS, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of

multiple myeloma and other hematological tumors. *J Immunol*. 2011;186(3):1840-1848. doi:10.4049/jimmunol.1003032
6. Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in vitro comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. *Blood*. 2014;124(21):3474. doi:10.1182/blood.V124.21.3474.3474
7. Overdijk MB, Verploegen S, Bogels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs*. 2015;7(2):311-321. doi:10.1080/19420862.2015.1007813
8. Overdijk MB, Jansen JH, Nederend M, et al. The therapeutic CD38 monoclonal antibody daratumumab induces programmed cell death via Fcγ receptor-mediated cross-linking. *J Immunol*. 2016;197(3):807-813. doi:10.4049/jimmunol.1501351
9. Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes $CD38^{+}$ immune-regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*. 2016;128(3):384-394. doi:10.1182/blood-2015-12-687749
10. Adams HC III, Stevenaert F, Krejcik J, et al. High-parameter mass cytometry evaluation of relapsed/refractory multiple myeloma patients treated with daratumumab demonstrates immune modulation as a novel mechanism of action. *Cytometry A*. 2019;95(3):279-289. doi:10.1002/cyto.a.23693
11. Casneuf T, Adams HC III, van de Donk NWCJ, et al. Deep immune profiling of patients treated with lenalidomide and dexamethasone with or without daratumumab. *Leukemia*. 2021;35(2):573-584. doi:10.1038/s41375-020-0855-4
12. Clemens PL, Yan X, Lokhorst HM, et al. Pharmacokinetics of daratumumab following intravenous infusion in relapsed or refractory multiple myeloma after prior proteasome inhibitor and immunomodulatory drug treatment. *Clin Pharmacokinet*. 2017;56(8):915-924. doi:10.1007/s40262-016-0477-1
13. Xu XS, Yan X, Puchalski T, et al. Clinical implications of complex pharmacokinetics for daratumumab dose regimen in patients with relapsed/refractory multiple myeloma. *Clin Pharmacol Ther*. 2017;101(6):721-724. doi:10.1002/cpt.577
14. Luo MM, Usmani SZ, Mateos MV, et al. Exposure-response and population pharmacokinetic analyses of a novel subcutaneous formulation of daratumumab administered to multiple myeloma patients. *J Clin Pharmacol*. 2021;61(5):614-627. doi:10.1002/jcph.1771
15. Xu XS, Dimopoulos MA, Sonneveld P, et al. Pharmacokinetics and exposure-response analyses of daratumumab in combination therapy regimens for patients with multiple myeloma. *Adv Ther*. 2018;35(11):1859-1872. doi:10.1007/s12325-018-0815-9
16. Usmani SZ, Nahi H, Mateos MV, et al. Subcutaneous delivery of daratumumab in relapsed or refractory multiple myeloma. *Blood*. 2019;134(8):668-677. doi:10.1182/blood.2019000667
17. San-Miguel J, Usmani SZ, Mateos MV, et al. Subcutaneous daratumumab in patients with relapsed or refractory multiple myeloma: part 2 of the open-label, multicenter, dose-escalation phase 1b study (PAVO). *Haematologica*. 2021;106(6):1725-1732. doi:10.3324/haematol.2019.243790
18. Gibiansky E, Brewster M, Chavanne C, Frey N, Jamois C. Comparison of population pharmacokinetics and exposure-response relationships of intravenous rituximab and subcutaneous rituxumab in patients with chronic lymphocytic leukemia. *Abstracts of the Annual Meeting of the Population Approach Group in Europe*. 24. Abstract 3604. 2015.
19. Quartino AL, Hillenbach C, Li J, et al. Population pharmacokinetic and exposure-response analysis for trastuzumab administered using a subcutaneous "manual syringe" injection or intravenously in women with HER2-positive early breast cancer. *Cancer Chemother Pharmacol*. 2016;77(1):77-88. doi:10.1007/s00280-015-2922-5
20. Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol*. 2020;7(5):e370-e380. doi:10.1016/S2352-3026(20)30070-3
21. Yan X, Clemens PL, Puchalski T, et al. Influence of disease and patient characteristics on daratumumab exposure and clinical outcomes in relapsed or refractory multiple myeloma. *Clin Pharmacokinet*. 2018;57(4):529-538. doi:10.1007/s40262-017-0598-1
22. DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) [US package insert]. Horsham, PA: Janssen Biotech, Inc; 2022.
23. Darzalex 20 mg/mL concentrate for solution for infusion. Summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004077/WC500207296.pdf. Accessed April 15, 2022.
24. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood*. 2017;130(8):974-981. doi:10.1182/blood-2017-05-785246
25. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(6):801-812. doi:10.1016/S1470-2045(21)00128-5
26. Alexander SPH, Kelly E, Mathie A, et al. The Concise Guide to PHARMACOLOGY 2021/22: introduction and other protein targets. *Br J Pharmacol*. 2021;178(suppl 1):S1-S26. doi:10.1111/bph.15537
27. Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(9):576-588. doi:10.1002/psp4.12224
28. Yan X, Clemens PL, Puchalski T, et al. Target-mediated drug disposition of daratumumab following intravenous infusion in relapsed or refractory multiple myeloma after prior proteasome inhibitors and immunomodulatory drugs: a population pharmacokinetic analysis. *Blood*. 2015;126(23):4222. doi:10.1182/blood.V126.23.4222.4222
29. Liu C, Yu J, Li H, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. *Clin Pharmacol Ther*. 2017;101(5):657-666. doi:10.1002/cpt.656
30. Cosson VF, Ng VW, Lehle M, Lum BL. Population pharmacokinetics and exposure-response analyses of trastuzumab in patients with advanced gastric or gastroesophageal junction cancer. *Cancer Chemother Pharmacol*. 2014;73(4):737-747. doi:10.1007/s00280-014-2400-5
31. Wang Y, Booth B, Rahman A, Kim G, Huang SM, Zineh I. Toward greater insights on pharmacokinetics and exposure-response relationships for therapeutic biologics in oncology drug development. *Clin Pharmacol Ther*. 2017;101(5):582-584. doi:10.1002/cpt.628
32. Kawakatsu S, Bruno R, Kågedal M, et al. Confounding factors in exposure-response analyses and mitigation strategies for monoclonal antibodies in oncology. *Br J Clin Pharmacol*. 2021;87(6):2493-2501. doi:10.1111/bcp.14662

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Dosne A-G, Li X, Luo MM, et al. Population pharmacokinetics and exposure–response analyses of daratumumab plus pomalidomide/dexamethasone in relapsed or refractory multiple myeloma. *Br J Clin Pharmacol*. 2022;1-16. doi:10.1111/bcp.15628