Adv Ther (2020) 37:1464–1478
https://doi.org/10.1007/s12325-020-01247-8

ORIGINAL RESEARCH

Split First Dose Administration of Intravenous Daratumumab for the Treatment of Multiple Myeloma (MM): Clinical and Population Pharmacokinetic Analyses

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Received: November 6, 2019 / Published online: February 20, 2020

ABSTRACT

Introduction: Daratumumab, a human immunoglobulin Gκ monoclonal antibody targeting CD38, is approved as monotherapy and in combination with standard-of-care regimens for multiple myeloma. In clinical studies, the median durations of the first, second, and subsequent intravenous infusions of daratumumab were 7.0, 4.3, and 3.4 h, respectively. Splitting the first intravenous infusion of daratumumab over 2 days is an approved alternative dosing regimen to reduce the duration of the first infusion and provide flexibility for patients and healthcare providers.

Methods: The feasibility of splitting the first 16-mg/kg infusion into two separate infusions of 8 mg/kg on Days 1 and 2 of the first treatment cycle was investigated in two cohorts [daratumumab, carfilzomib, and dexamethasone (D-Kd) and daratumumab, carfilzomib, lenalidomide, and dexamethasone (D-KRd)] of the phase 1b MMY1001 study. Additionally, a population pharmacokinetic (PK) analysis and simulations were used to compare the PK

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Electronic Supplementary Material The online version of this article (https://doi.org/10.1007/s12325-020-01247-8) contains supplementary material, which is available to authorized users.

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profiles of the split first dose regimen with the recommended single first dose regimens of daratumumab in previously approved indications.

Results: In MMY1001, following administration of the second half of a split first dose on Cycle 1 Day 2, postinfusion median (range) daratumumab concentrations were similar between split first dose [D-Kd, 254.9 (125.8–435.5) μg/ml; D-KRd, 277.2 (164.0–341.8) μg/ml; combined, 256.8 (125.8–435.5) μg/ml] and single first dose [D-Kd, 319.2 (237.5–394.7) μg/ml]. At the end of weekly dosing, median (range) Cycle 3 Day 1 preinfusion daratumumab concentrations were similar between split first dose [D-Kd, 663.9 (57.7–1110.7) μg/ml; D-KRd, 575.1 (237.9–825.5) μg/ml; combined, 639.2 (57.7–1110.7) μg/ml] and single first dose [D-Kd, 463.2 (355.9–792.9) μg/ml]. The population PK simulations demonstrated virtually identical PK profiles after the first day of treatment for all approved indications and recommended dosing schedules of daratumumab.

Conclusion: These data support the use of an alternative split first dose regimen of intravenous daratumumab for the treatment of MM.

Trial Registration: ClinicalTrials.gov number, NCT01998971.

Keywords: Clinical pharmacology; Daratumumab; Intravenous infusion; Multiple myeloma; Pharmacokinetics; Single first dose; Split first dose

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Key Summary Points

Splitting the first infusion of intravenous daratumumab over 2 days is an approved alternative dosing regimen to reduce the duration of the first infusion and provide flexibility for patients and healthcare providers, without increasing the rate of infusion-related reactions.

Pharmacokinetics (PK) data from the MMY1001 study and the population PK simulation demonstrate that daratumumab concentration profiles were comparable following completion of administration of the first 16-mg/kg dose of daratumumab regardless of whether it was administered as a split first dose or a single first dose.

These findings support the use of an alternative split first dose regimen of intravenous daratumumab for the treatment of multiple myeloma.

INTRODUCTION

Daratumumab is a human immunoglobulin Gκ (IgGκ) monoclonal antibody targeting CD38 with a direct on-tumor [1–4] and immunomodulatory [5–7] mechanism of action. Daratumumab 16 mg/kg administered intravenously (IV) demonstrates activity as monotherapy and provides clinical benefit when combined with standard-of-care regimens for the treatment of multiple myeloma (MM) across lines of therapy [10–14]. Based on the findings of several phase 3 clinical studies, daratumumab (16 mg/kg) in combination with lenalidomide and dexamethasone (D-Rd), bortezomib and dexamethasone (D-Vd), and bortezomib, melphalan, and prednisone (D-VMP) has received approval for the treatment of patients with relapsed/refractory MM (D-Rd and D-Vd) or transplant-ineligible newly diagnosed MM (D-Rd and D-VMP) in many countries

worldwide. Daratumumab is also approved as monotherapy in many countries and in combination with pomalidomide and dexamethasone (D-Pd) in the USA.

Infusion-related reactions have been reported in patients treated with IV daratumumab (16 mg/kg), which are predominately grade 1 or 2 in severity and occur primarily during the first daratumumab infusion [9]. As early clinical data demonstrated an association between a higher rate of infusion-related reactions and a faster infusion rate of daratumumab, a prolonged infusion time for the first dose of daratumumab is necessary to reduce the incidence of infusion-related reactions. In clinical studies, the median durations of the first, second, and subsequent daratumumab infusions were 7.0, 4.3, and 3.4 h, respectively [9]. The first daratumumab infusion is administered in a larger infusion volume (1000 ml) and at a slower initial infusion rate (50 ml/h) compared with the second (500 ml; 50 ml/h) and subsequent infusions (500 ml; 100 ml/h), thus prolonging the infusion time [9].

Splitting the first infusion of daratumumab over 2 days has been proposed as an alternative dosing regimen to reduce the duration of the first infusion and reduce treatment burden for patients and healthcare providers. A split first dose of daratumumab was evaluated in two cohorts of a phase 1b MMY1001 study of daratumumab in combination with standard-of-care regimens in MM (NCT01998971). These analyses demonstrated that the split first dose of daratumumab is feasible and may improve patient convenience for initial dosing [15, 16]. However, it is unknown whether patients can achieve effective daratumumab serum concentrations with a split first dose regimen. Data from monotherapy studies show that daratumumab exhibits nonlinear pharmacokinetics (PK) consistent with target-mediated drug disposition [17]. The recommended dose regimen of 16 mg/kg weekly for 8 weeks rapidly saturates target-mediated clearance, and subsequent dosing every 2 weeks for 16 weeks and every 4 weeks thereafter maintains target saturation. Population PK and exposure-response analyses have demonstrated a strong association between daratumumab concentration (maximum trough concentration [C_{trough}]) and efficacy in patients with relapsed/refractory MM [18, 19]. A maximum C_{trough} of 274 μg/ml was associated with 90% maximal effect on overall response rate, and a concentration of 236 μg/ml was required to achieve 99% model-predicted target (CD38) saturation [18]. These data highlight the importance of attaining daratumumab serum concentrations with a split first dose regimen that are similar to the approved single first dose regimen.

The objective of this study was to present PK analysis results of splitting the first daratumumab 16-mg/kg IV dose into two separate infusions of 8 mg/kg on Days 1 and 2 of the first treatment cycle. This dosing regimen was given to patients in the daratumumab, carfilzomib, and dexamethasone (D-Kd) and daratumumab, carfilzomib, lenalidomide, and dexamethasone (D-KRd) arms of the phase 1b MMY1001 study [15, 16]. In addition, population PK analyses and simulations were used to compare the PK profiles of the split first dose regimen with the recommended single first dose regimens of daratumumab in previously approved indications.

METHODS

MMY1001 Study Design and Treatment

MMY1001 is a phase 1b, open-label, nonrandomized, multicenter study evaluating the safety, tolerability, and dosing regimen of daratumumab in combination with established treatment regimens for patients with newly diagnosed MM or relapsed/refractory MM. Eligible patients were ≥ 18 years of age with measurable documented MM and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. The split first dose administration for daratumumab was investigated in the D-KRd and D-Kd cohorts of MMY1001. Patients with newly diagnosed MM were enrolled in the D-KRd cohort irrespective of transplant eligibility. Patients in the D-Kd cohort had relapsed/refractory MM with one to three prior lines of therapy including bortezomib and an immunomodulatory agent. Daratumumab 16 mg/kg IV was administered to D-KRd and D-Kd cohorts weekly for Cycles 1 and 2,

every 2 weeks for Cycles 3–6, and every 4 weeks for the remaining cycles. In the D-Kd arm of MMY1001, ten patients received the first daratumumab dose as a single infusion [16 mg/kg (1000 ml) on Day 1 Cycle 1] and 75 patients received a split first dose [8 mg/kg (500 ml) on Days 1–2 Cycle 1]. In the D-KRd arm, all patients received a split first dose of daratumumab.

Pharmacokinetic data from the D-Kd and D-KRd cohorts (n = 107) were used for PK analysis. Serum samples were collected pre- and postinfusion of daratumumab on Day 1 of Cycle 1 through Cycle 4 and then 3 and 9 weeks posttreatment for all patients in the D-Kd and D-KRd cohorts. Serum samples were also collected pre- and postinfusion on Cycle 1 Day 2 for patients receiving the split first dose in the D-Kd and D-KRd cohorts. An enzyme-linked immunosorbent assay (ELISA) validated in 2009 by Bio Analytical Research Corporation (BARC) Global Central Laboratory (Ghent, Belgium) was used to determine serum daratumumab concentrations in previous studies. In 2014, the BARC ELISA PK method was transferred to Janssen Research & Development, LLC (Spring House, PA, USA), and successfully cross-validated for reproducibility at two separate laboratories. The transferred ELISA PK method was used by Janssen Research & Development, LLC, to determine daratumumab concentrations in human serum in subsequent analyses of daratumumab studies. In general, the ELISA method was validated according to the European Medicines Agency, the US Food and Drug Administration, bioanalytical method validation guidance, and industry white papers (EMEA/CHMP/EWP 2011, Guidance for Industry 2018) [20, 21]. The lowest quantifiable concentration of daratumumab in a sample was 0.2 μg/ml, and the upper limit of quantification was 145.8 μg/l at a 1:40 dilution. The inter-assay variability across the standard curve range was $< 10\%$.

Serum daratumumab concentrations were summarized using descriptive statistics and presented as arithmetic mean, standard deviation, and coefficient of variation. PK values are summarized by nominal time and presented as arithmetic mean, standard deviation (SD), and coefficient of variation.

Population PK Analysis

The population PK analysis used nonlinear mixed-effects modeling and simulation to compare the PK profile of the daratumumab split first dose regimen (8 mg/kg on Cycle 1 Day 1 and Cycle 1 Day 2) with approved or recommended single first dose regimens (16 mg/kg on Cycle 1 Day 1) using individual PK parameters of patients with MM from seven clinical studies of daratumumab, including daratumumab monotherapy studies [GEN501 (NCT00574288) and SIRIUS (NCT01985126); n = 223]; D-Rd treatment studies [GEN503 (NCT01615029) and POLLUX (NCT02076009); n = 326]; D-Vd treatment studies [CASTOR (NCT02136134) and MMY1001 (NCT01998971); n = 246]; D-VMP treatment studies [MMY1001 and ALCYONE (NCT02195479); n = 352]; MMY1001 D-Pd treatment arm (n = 99), and MMY1001 D-Kd and D-KRd treatment arms (n = 107), all of which have been described in detail previously and are briefly summarized in Online Resource 1 [10–16, 22–24].

The individual PK parameters for D-Kd and D-KRd were generated using a newly developed, nonlinear, mixed-effects population PK model in the current report. Serum concentration-time data were used for nonlinear mixed-effects modeling using NONMEM (ICON plc, version 7 or higher). The population PK model included a two-compartment structure with parallel linear and Michaelis-Menten nonlinear eliminations [25], where linear clearance represents the nonspecific clearance for IgG, and the Michaelis-Menten elimination represents the saturable target-mediated clearance. The interpatient variability in structural parameters was modeled with an exponential term to ensure positive values of individual parameters, and an additive model was used to model residual variability. The final covariate model included body weight, albumin, type of myeloma, and sex as significant yet non–clinically relevant covariates. PK parameter estimates for individual patients treated with other regimens were obtained from previously developed population PK models [18, 19, 25]. Simulations were performed to predict the PK profiles for all patients who had participated in previous daratumumab

studies and to compare the difference in PK between the split- and single-first dose of daratumumab among those patients. Therefore, we mimicked a cross-over design, so each patient was assumed to receive both split- and single-first dose approaches in a sequential manner. The cross-over design removes the influence of between-patient variability and enables a better comparison of PK for both dosing approaches. The empirical Bayesian estimates of PK parameters for each patient were used for simulations. Simulations were conducted for individual treatments or indications with dosing schedules for daratumumab monotherapy, D-Rd, D-Pd, D-Kd, and D-KRd that consisted of daratumumab 16 mg/kg given once weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter. For D-Vd, the dosing schedule consisted of daratumumab 16 mg/kg given every week for 9 weeks, every 3 weeks for 15 weeks, and every 4 weeks thereafter. The D-VMP dosing schedule consisted of daratumumab 16 mg/kg given every week for 6 weeks, every 3 weeks for 48 weeks, and every 4 weeks thereafter.

Compliance with Ethics Guidelines

The individual protocols and amendments for each study included in this report were reviewed and approved by affiliated local independent ethics committees or internal review boards (see Online Resource 2 for a list of committees for MMY1001). Studies were conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written consent prior to any study-specific procedures.

RESULTS

Patient and Disease Characteristics

The PK-evaluable population was composed of 107 patients in the D-Kd ($n = 85$) and D-KRd ($n = 22$) cohorts of MMY1001. A total of 97 patients received a split first dose of daratumumab 8 mg/kg on Cycle 1 Day 1 and Cycle 1 Day 2 (D-Kd, $n = 75$; D-KRd, $n = 22$). An additional ten patients in the D-Kd cohort received the standard single first dose regimen of daratumumab 16 mg/kg on Cycle 1 Day 1. Patient demographics and baseline disease characteristics are summarized in Table 1. Briefly, the majority of patients in both treatment cohorts had an ECOG score < 2 (D-Kd, 91.8%; D-KRd, 95.5%). Patients with relapsed/refractory MM in the D-Kd cohort were numerically older (median: 66 years of age) than patients with newly diagnosed MM in the D-KRd cohort (median: 60 years of age). However, the impact of the difference in age between the populations was minimal since the relative difference in PK from the split- and single-first dose regimens were compared and the PK parameters from each patient were used for simulations of both the single-first and split-dose regimens.

PK Analysis of MMY1001 Split and Single First Dose Cohorts

In MMY1001, measured daratumumab Cycle 1 Day 1 postinfusion median (range) concentrations after the first half (8 mg/kg) of a split first dose [D-Kd, 151.5 (82.5–345.0) μg/ml; D-KRd, 177.8 (121.9–215.7) μg/ml; combined, 156.7 (82.5–345.0) μg/ml] were lower than the concentrations after a 16-mg/kg single first dose [D-Kd, 319 (237.5–394.7) μg/ml; Table 2]. Following administration of the second half (8 mg/kg) of a split first dose on Cycle 1 Day 2, postinfusion median (range) daratumumab concentrations were similar between patients who received a split first dose [D-Kd, 254.9 (125.8–435.5) μg/ml; D-KRd, 277.2 (164.0–341.8) μg/ml; combined, 256.8 (125.8–435.5) μg/ml] and those who received a single first dose (Table 2; Fig. 1). At the end of weekly dosing, median (range) Cycle 3 Day 1 preinfusion daratumumab concentrations ($C_{troughs}$) were similar between patients who received a split first dose [D-Kd, 663.9 (57.7–1110.7) μg/ml; D-KRd, 575.1 (237.9–825.5) μg/ml; combined, 639.2 (57.7–1110.7) μg/ml] and those who

Table 1 Demographics and Baseline Disease Characteristics

Characteristic	D-Kd (*N* = 85)	D-KRd (*N* = 22)
Age, years		
Median (range)	66 (38–85)	60 (34–74)
Category, *n* (%)		
< 65	36 (42.4)	15 (68.2)
65 to < 75	41 (48.2)	7 (31.8)
≥ 75	8 (9.4)	0 (0.0)
Gender		
Male	46 (54.1)	12 (54.5)
Female	39 (45.9)	10 (45.5)
Race		
White	68 (80.0)	19 (86.4)
Black or African American	3 (3.5)	1 (4.5)
Asian	3 (3.5)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	1 (4.5)
Not reported	11 (12.9)	1 (4.5)
Height, cm		
Median (range)	165.0 (141.5–185.4)	172.9 (153.7–193.0)
Weight, kg		
Median (range)	70.0 (45.0–160.8)	79.9 (55.1–144.2)
ECOG performance status, *n* (%)		
0	32 (37.6)	12 (54.5)
1	46 (54.1)	9 (40.9)
2	7 (8.2)	1 (4.5)

D-Kd daratumumab/carfilzomib/dexamethasone, *D-KRd* daratumumab/carfilzomib/lenalidomide/dexamethasone, *ECOG* Eastern Cooperative Oncology Group

received a single first dose [D-Kd, 463.2 (355.9–792.9) μg/ml; Table 2].

Serum concentrations at the end of infusion on Days 1 and 2 of Cycle 1 and maximum serum C_{trough} (at the end of weekly dosing) were compared between the split first dose regimens and the single first dose regimens from the MMY1001 D-Kd and D-KRd cohorts with other single first dose daratumumab combination studies, MMY1001, GEN503, POLLUX, CASTOR, and ALCYONE (Online Resource 3). Similar concentrations were observed after administration of the first total dose of 16 mg/kg per patient across monotherapy and combination therapies, indicating that the regimen has no meaningful impact on the concentration of daratumumab after Cycle 1 Day 1. The maximum C_{trough} at the end of weekly dosing was also similar (< 10% difference in maximum C_{trough}) across studies, regardless of the split or single first dose and dosing regimen.

Table 2 Summary of Daratumumab Serum Concentrations Over Time in MMY1001 D-Kd and D-KRd Dose Cohorts

Sampling time point	D-Kd		D-KRd	Combined
	Single dose	Split dose	Split dose	Split dose
PK-evaluable patients, *n*	10	75	22	97
C1D1 postinfusion[a]				
n	8	71	15	86
Median (range), μg/ml	319.2 (237.5–394.7)	151.5 (82.5–345.0)	177.8 (121.9–215.7)	156.7 (82.5–345.0)
CV (%)	15.3	31.5	16.8	29.3
C1D2 preinfusion[b]				
n	NA	65	16	81
Median (range), μg/ml	–	110.5 (0.0–284.9)	118.0 (61.2–169.2)	111.6 (0.0–284.9)
CV (%)	–	37.9	24.5	35.4
C1D2 postinfusion[a]				
N	NA	69	18	87
Median (range), μg/ml	–	254.9 (125.8–435.5)	277.2 (164.0–341.8)	256.8 (125.8–435.5)
CV (%)	–	28.2	20.8	26.7
C2D1 preinfusion[b]				
N	10	63	21	84
Median (range), μg/ml	335.8 (186.6–556.4)	380.7 (0.0–721.6)	329.8 (112.1–473.4)	354.7 (0.0–721.6)
CV (%)	34.5	49.4	32.9	47.0
C2D1 postinfusion[a]				
N	9	64	15	79
Median (range), μg/ml	726.6 (523.1–911.6)	688.6 (0.0–1202.4)	692.4 (458.8–961.0)	688.9 (0.0–1202.4)
CV (%)	22.1	36.4	23.1	34.3
C3D1 preinfusion[b]				
N	9	52	19	71
Median (range), μg/ml	463.2 (355.9–792.9)	663.9 (57.7–1110.7)	575.1 (237.9–825.5)	639.2 (57.7–1110.7)
CV (%)	26.5	41.4	30.7	39.1
C3D1 postinfusion[a]				
N	9	52	14	66
Median (range), μg/ml	844.1 (725.4–1176.0)	916.0 (36.9–1711.3)	939.3 (638.4–1301.0)	926.0 (36.9–1711.3)
CV (%)	18.9	36.8	17.9	33.5
C4D1 preinfusion[b]				
N	7	24	21	45
Median (range), μg/ml	509.1 (291.2–743.5)	613.0 (92.3–1019.3)	457.3 (146.1–768.1)	523.0 (92.3–1019.3)
CV (%)	30.9	41.8	33.2	39.2

Table 2 continued

Sampling time point	D-Kd		D-KRd	Combined
	Single dose	Split dose	Split dose	Split dose
C4D1 postinfusion[a]				
N	8	24	11	35
Median (range), μg/ml	918.6 (646.5–1142.6)	962.0 (347.0–1630.2)	939.4 (776.6–1205.0)	939.4 (347.0–1630.2)
CV (%)	19.2	31.3	15.3	27.0

D-Kd daratumumab/carfilzomib/dexamethasone, *D-KRd* daratumumab/carfilzomib/lenalidomide/dexamethasone, *PK* pharmacokinetics, *C* cycle, *D* day, *SD* standard deviation, *CV* coefficient of variation, *NA* not applicable

[a] Postinfusion PK sampling time window was up to 5 min after the end of infusion

[b] Preinfusion PK sampling time window was up to 2 h prior to the start of the infusion or administration of the backbone medications

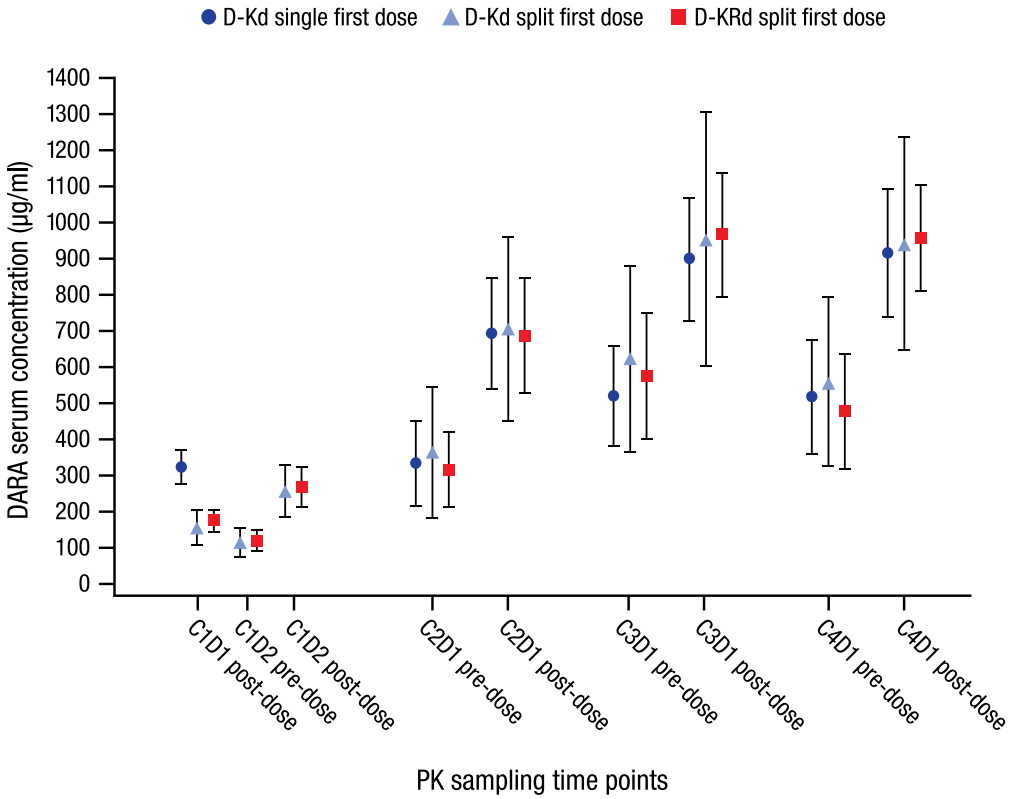

Fig. 1 Mean daratumumab serum concentrations (μg/ml) among PK-evaluable patients in MMY1001 D-Kd and D-KRd single/split first daratumumab dose cohorts. Values are mean ± SD. *PK* pharmacokinetic, *D-Kd* daratumumab/carfilzomib/dexamethasone, *D-KRd* daratumumab/carfilzomib/lenalidomide/dexamethasone, *DARA* daratumumab, *C* Cycle, *D* Day, *SD* standard deviation

Population PK Analysis

A prediction-corrected visual predictive check of the final population PK model was performed to compare the simulation and observed daratumumab concentrations over time (Online Resource 4). The visual predictive check plot showed good agreement between the simulated concentrations and the individual observed concentrations (Online Resource 4). The estimated inter-patient variability adequately captured the observed variability.

Simulation of daratumumab PK following the split first dose and single first dose regimens was conducted using individual PK parameters of patients with MM from seven clinical studies of daratumumab. Regimens included daratumumab monotherapy, D-Rd, D-Vd, D-Pd, D-VMP, D-Kd, and D-KRd. The split first dose and single first dose regimens were virtually identical with respect to their overall PK profiles (Fig. 2a, Online Resource 5). Simulated PK profiles of the split first dose and single first dose regimens varied only during the first day of treatment (Cycle 1 Day 1) when the dosing regimens were different (8 mg/kg versus 16 mg/kg; Fig. 2b). Differences in simulated PK profiles were minimal following the second split dose on Cycle 1 Day 2. The difference in concentrations between the split-dose and single-infusion regimens was reduced to < 1% for the majority of patients by Week 4 (Fig. 3).

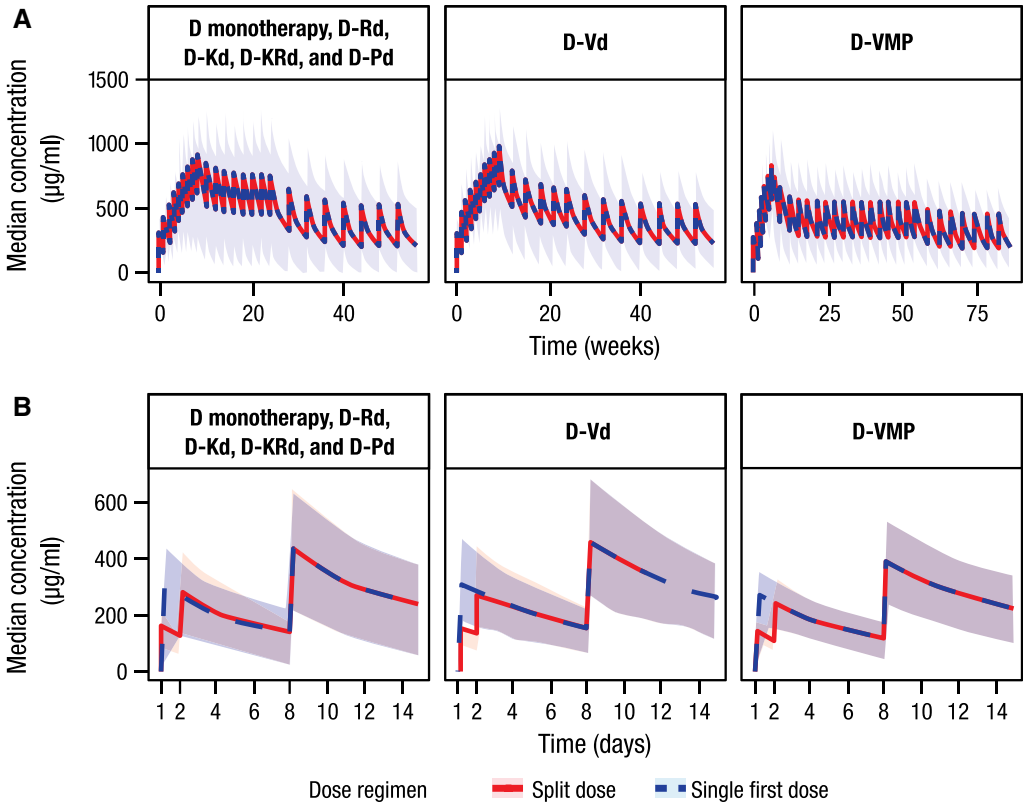

Fig. 2 Simulated daratumumab concentration-time profiles (**a**) and simulated daratumumab concentration-time profiles for the first 2 weeks (**b**) for the split- and single-first dose of daratumumab 16 mg/kg in patients who received daratumumab monotherapy, D-Rd, D-Kd, D-KRd, and D-Pd (left); D-Vd (middle); and D-VMP (right) regimens. The red solid and blue dashed lines represent the median, and the shaded regions are bounded by the 2.5th and 97.5th percentiles of the simulation. *D* daratumumab, *D-Rd* daratumumab/lenalidomide/dexamethasone, *D-Kd* daratumumab/carfilzomib/dexamethasone, *D-KRd* daratumumab/carfilzomib/lenalidomide/dexamethasone, *D-Pd* daratumumab/pomalidomide/dexamethasone, *D-Vd* daratumumab/bortezomib/dexamethasone, *D-VMP* daratumumab/bortezomib/melphalan/prednisone

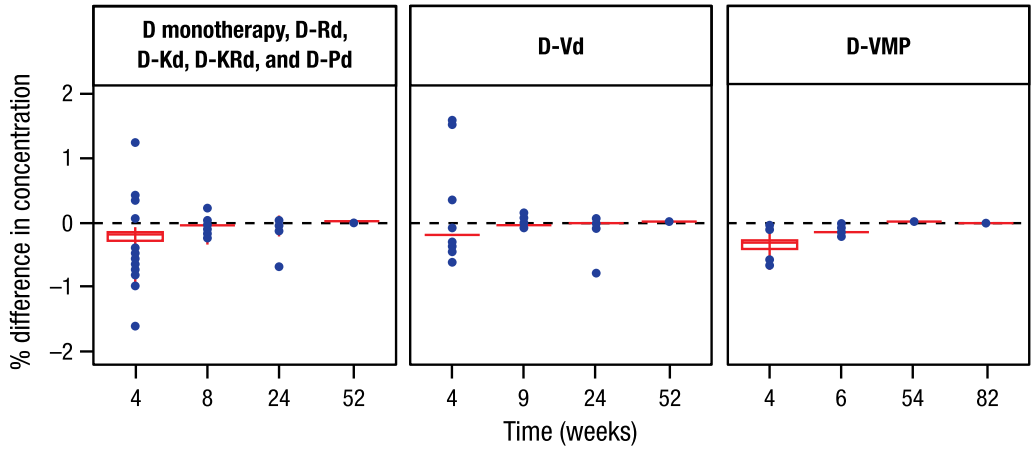

Fig. 3 Boxplot comparison of percent difference in simulated daratumumab C_{trough} in patients who received daratumumab 16-mg/kg monotherapy, D-Rd, D-Kd, D-KRd, and D-Pd (left); D-Vd (middle); and D-VMP (right) regimens. Percent difference in concentration is calculated by the following formula: (SINGLE–SPLIT DOSE)/SINGLE × 100%, where SINGLE is the daratumumab concentration for single first dose and SPLIT DOSE is the daratumumab concentration for split first dose. A negative % difference in concentration indicates that the daratumumab concentration of the single first dose is less than the concentration of the split first dose. C_{trough}, trough concentration; *D* daratumumab, *D-Rd* daratumumab/lenalidomide/dexamethasone, *D-Kd* daratumumab/carfilzomib/dexamethasone, *D-KRd* daratumumab/carfilzomib/lenalidomide/dexamethasone, *D-Pd*, daratumumab/pomalidomide/dexamethasone, *D-Vd* daratumumab/bortezomib/dexamethasone, *D-VMP* daratumumab/bortezomib/melphalan/prednisone

The final model of the monotherapy studies was used to fit data for daratumumab serum concentration versus time. The model-based covariate analysis identified body weight, baseline albumin level, and type of myeloma (IgG versus non-IgG) as statistically significant covariates on linear clearance, whereas body weight and sex were identified as statistically significant covariates on the volume of distribution in the central compartment. Parameter estimates of the final covariate model are shown in Online Resource 6. The estimated linear clearance and volume of distribution parameters were very close to the estimates from previous studies. The condition number of the final model was 27.80, indicating the final covariate model was appropriately parameterized.

DISCUSSION

Pharmacokinetic data from MMY1001 and the population PK analysis suggest that, with the exception of the PK profile during the first day of treatment, a split or single first dose of IV daratumumab provides virtually identical PK for all approved indications and recommended dosing regimens. Because the transient difference in daratumumab serum concentration on Cycle 1 Day 1 is not expected to have any impact on overall clinical outcomes, these findings suggest that the split first dose regimen of IV daratumumab is feasible and provides an alternative flexible dosing strategy for patients and healthcare providers.

The primary objective of this modeling and simulation study was to use simulation to compare single first dose versus split first dose. An appropriate design of the simulation study is a cross-over design, so each patient was assumed to receive both split and single first dose approaches in a sequential manner. The cross-over design allows removing the influence by between-patient variability and better comparison of PK for both dosing approaches. This can be achieved without pooling all the studies as individual parameter estimates were available from previous models. Also, different patient

populations exhibited some difference in PK behaviors, so pooling all studies may mask these differences.

Among patients in the PK-evaluable population, 97 received a split first dose of daratumumab versus only ten patients who received the standard single first dose regimen of daratumumab. Based on the differences in the number of patients in each dosing group, shrinkage was evaluated and determined to be < 20%. In addition, since the relative difference in PK from the split- and single-first dose regimens were compared and the PK parameters from each patient were used for simulations of both the split first dose and standard single dose, the impact of shrinkage on the relative difference may have been cancelled out.

The PK profile for the split first dose regimen of daratumumab was similar to the PK profiles of daratumumab demonstrated in previous monotherapy and combination therapy studies, regardless of the population treated. After the first total dose of 16 mg/kg, mean daratumumab serum concentrations (Table 2) for the split first dose (Cycle 1 Day 2) and single first dose (Cycle 1 Day 1) regimens were similar to those observed after the first dose of daratumumab monotherapy in SIRIUS (313 μg/ml) and daratumumab combination therapy in CASTOR (D-Vd; 318 μg/ml) and POLLUX (D-Rd; 329 μg/ml) [17]. The consistency of daratumumab exposure across split- and single-first dose regimens continued through the end of weekly dosing (Cycle 3 Day 1) and was comparable to daratumumab monotherapy in SIRIUS (574 μg/ml) and D-Rd combination therapy in POLLUX (608 μg/ml) [17]. At the end of weekly dosing, C_{trough} for the split dose regimen was also above the effective C_{trough} of daratumumab monotherapy (274 μg/ml) [18]. Overall, these data support that daratumumab may be administered as a split dose on Day 1 and Day 2 of Cycle 1.

Results from the population PK analysis were consistent with the clinical PK data from MMY1001. The population PK simulation implemented a cross-over design and allowed for comparison of daratumumab split first dose PK with single first dose PK within the same individual patient. The simulations overcame the relatively small sample size in the single first dose D-Kd group for the clinical PK analysis and the limited PK sampling over time in this phase 1 study. In addition, the cross-over design in the simulation removed the between-patient variability from the comparison of the two dosing approaches and therefore circumvented the limitations caused by cross-study heterogeneity in previous clinical studies, such as sample sizes, phases of drug testing, and eligibility criteria. Using data from seven clinical studies, the simulation results suggest that the PK profiles of the split first dose regimen and single first dose regimen should provide virtually identical PK, with the exception of the PK profile during the first day of treatment, for all approved indications and recommended dosing regimens.

Previous exposure-response analysis for daratumumab monotherapy and combination therapy studies has demonstrated a strong correlation between efficacy endpoints, including overall response rate and progression-free survival as well as daratumumab serum exposure [18, 19]. In contrast, no apparent relationship between serum drug exposure and adverse events was observed [18, 19]. Given that the PK profile, including the C_{trough} at the end of weekly dosing, was similar between the split first dose and single first dose regimens, it is anticipated that the efficacy and safety following the split first dose regimen would be similar to that of the single first dose regimen.

Clinical data from MMY1001 D-KRd and D-Kd cohorts have demonstrated that split first dosing of daratumumab is well tolerated, with safety profiles consistent with previous reports of daratumumab, KRd, and Kd [15, 16]. No increase in the rate of infusion-related reactions was observed with split compared with single first dosing of daratumumab in MMY1001 D-KRd and D-Kd cohorts [15, 16]. On Cycle 1 Day 1, infusion-related reactions were observed in 37% and 23% of patients treated with split first dose D-Kd and D-KRd, respectively, compared with 1% and 5% of patients who received D-Kd and D-KRd, respectively, on Cycle 1 Day 2 [15, 16]. Among patients treated with a single first dose of D-Kd, 50% experienced infusion-related reactions on Cycle 1 Day 1 [15, 16]. Findings from the MMY1001 study and the PK simulations led to the approval of the split first

dose as an alternative daratumumab dosing protocol in many countries [26, 27]. Furthermore, a real-world observational study of patients with MM who received daratumumab in US community oncology clinics found that utilization of the split first dose of daratumumab increased over time and was used more frequently than the single first dose regimen by the end of the study period [28]. The split first dose was associated with a shorter infusion duration on Day 1 and did not increase the rate of infusion reactions compared with the single first dose regimen [28], supporting the use of split first dosing in patients with MM. Several clinical studies using the split first dosing of daratumumab are also ongoing, including the phase 2 LYRA (NCT02951819) study of daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone in newly diagnosed MM and relapsed MM [29] and the phase 3 CANDOR (NCT03158688) study of D-Kd versus Kd in patients with relapsed/refractory MM.

CONCLUSIONS

These data suggest that daratumumab concentration profiles were comparable following completion of administration of the first 16-mg/kg dose of daratumumab, regardless of whether it was administered as a split first dose or a single first dose, and support the use of a split first dose regimen as an alternative to the single first dose regimen of daratumumab for the treatment of patients with MM.

ACKNOWLEDGMENTS

The authors thank the patients who participated in the MMY1001, GEN501, SIRIUS, GEN503, POLLUX, CASTOR, and ALCYONE studies and their families as well as study coinvestigators, research nurses, and coordinators at each of the clinical sites.

Funding. This study was sponsored by Janssen Research & Development, LLC. Janssen Global Services, LLC, funded the Rapid Service and Open Access Fees.

Medical Writing and Editorial Assistance. Editorial and medical writing support was provided by J. Matthew Kuczmarski, PhD, of MedErgy and funded by Janssen Global Services, LLC.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Prior Presentation. These data were previously presented, in part, at the 60th Annual Meeting of the American Society of Hematology; 1–4 December 2018; San Diego, CA.

Disclosures. Man Luo, Yu-Nien Sun, Honghui Zhou, Ivo Nnane, William Deraedt, Ming Qi, Jon Ukropec, and Pamela L. Clemens are employees of Janssen and hold equity in Johnson & Johnson. Xu Steven Xu was an employee of Janssen at the time of the study and manuscript preparation and may hold equity in Johnson & Johnson; his current affiliation is Genmab US Inc, Princeton, NJ, USA. Philippe Moreau served as a consultant for and received honoraria from Amgen, Celgene, Janssen, Takeda, Bristol-Myers Squibb, Novartis, Millennium, and Onyx Pharmaceuticals. Saad Z. Usmani served as a consultant for AbbVie, Amgen, Celgene, Genmab, Merck, Mundi-Pharma, and Seattle Genetics; received research funding from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Merck, Pharmacyclics, and Takeda; and served as a member of the board of directors or advisory committees for and received research funding from Sanofi. Sagar Lonial received research funding from Amgen. Andrzej Jakubowiak served as a consultant for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Juno, Karyopharm, SkylineDx, and Takeda. Albert Oriol served as a consultant, as a member of the board of directors or advisory committees, and as a member of a speaker's bureau for Janssen, Celgene, Amgen, and

Takeda. Amrita Krishnan served as a consultant for Janssen and Celgene; was a member of a speaker's bureau for Janssen, Sutro, Onyx Pharmaceuticals, Takeda, and Celgene; and holds equity in Celgene. Joan Bladé received honoraria from Janssen.

Compliance With Ethics Guidelines. The individual protocols and amendments for each study included in this report were reviewed and approved by affiliated local independent ethics committees or internal review boards (see Online Resource 2 for a list of committees for MMY1001). Studies were conducted in accordance with 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 provided written consent prior to any study-specific procedures.

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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