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ARTICLE

PK/PD modeling analysis for dosing regimen selection of isatuximab as single agent and in combination therapy in patients with multiple myeloma

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Abstract

This analysis describes the pharmacokinetic/pharmacodynamic (PK/PD) modeling framework that supported selection of the isatuximab (anti-CD38 monoclonal antibody) dosing regimen alongside its early clinical development in patients with relapsed/refractory multiple myeloma (RRMM). The PK/PD mathematical model characterized the variations of patient serum M-protein concentrations, the primary marker of tumor burden in multiple myeloma (MM). Three separate PK/PD models were built sequentially as data became available from phase I clinical trials. The primary PK/PD analysis was initiated using monotherapy phase I study data (n = 122), followed by analysis of data collected from phase Ib combination studies with lenalidomide and dexamethasone (Rd, $n = 40$) and then with pomalidomide and dexamethasone (Pd, $n = 31$). Using the PK/PD model, abnormal "myeloma" protein (M-protein) profiles under different isatuximab dosing regimens were simulated. Overall, simulations revealed that regimens which included a loading period of four weekly administrations followed by administration every 2 weeks thereafter (QW4-Q2W), reduced M-protein levels more than a Q2W regimen without a loading period. For isatuximab monotherapy, a 20 mg/kg dose induced greater reduction in serum M-protein levels compared with doses equal or lower than 10 mg/kg. For isatuximab in combination with either Rd or Pd, simulations yielded no substantial benefit in terms of M-protein reduction between isatuximab 10 mg/kg and 20 mg/kg. These PK/PD analyses supported the use of isatuximab 10 mg/kg QW4-Q2W in combination with Pd in the phase III trial.

K.K. and R.E.-C. contributed equally to this work.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Serum M-protein levels, which are produced in excess by an abnormal clonal proliferation of myeloma plasma cells, are a marker of tumor burden in patients with multiple myeloma (MM).

WHAT QUESTION DID THIS STUDY ADDRESS?

To determine the recommended dose regimen for isatuximab monotherapy and combination therapy with either lenalidomide and dexamethasone or pomalidomide and dexamethasone, to be used in future clinical studies assessing the safety and/or efficacy of isatuximab in patients with MM.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The pharmacokinetic/pharmacodynamic (PK/PD) models developed, including dropout data, adequately describe longitudinal M-protein-time profiles and provide a relevant quantitative tool to select appropriate dose regimens for both monotherapy and combination settings.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The PK/PD models developed in three separate studies provide a better understanding of longitudinal M-protein kinetics, and, hence, are an important step toward finding a dose regimen for future clinical studies.

INTRODUCTION

Multiple myeloma (MM) is a neoplastic disease characterized by excessive proliferation of malignant plasma cells in the bone marrow.[1] The overgrowth of malignant cells leads to multiple disorders in hematopoiesis (anemia, leukopenia, and thrombocytopenia), deficiencies in organ functions as well as infections and bone lesions.[2,3] Myeloma plasma cells secrete a nonfunctional protein usually labeled M-protein, which is abundantly secreted in the peripheral blood upon disease progression. The main diagnostic criteria, per International Myeloma Working Group (IMWG), for MM are the presence of a M-protein component (e.g., entire protein or fragments) in serum and/or urine plus clonal plasma cells in the bone marrow.[4,5]

Conventional MM treatments comprise chemotherapies (e.g., melphalan and cyclophosphamide), proteasome inhibitors (e.g., bortezomib and carfilzomib), corticosteroids, and immunomodulatory drugs (e.g., lenalidomide and pomalidomide).[6-10] Recently, monoclonal antibodies, such as daratumumab, elotuzumab, and isatuximab, have improved treatment outcomes in relapsed/refractory MM (RRMM) as monotherapy and when combined with conventional therapies.[11-14]

Isatuximab is an IgG1 monoclonal antibody that binds to a specific CD38 epitope, targeting a different amino-acid sequence than daratumumab. Based on the phase III ICARIA-MM study, isatuximab (Sarclisa®) is approved in a number of countries in combination with pomalidomide/dexamethasone (Pd) for the treatment of patients with RRMM who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor.[14] Based on the phase III IKEMA study, isatuximab, to date, is also approved in combination with carfilzomib/dexamethasone in the United States for the treatment of patients with relapsed MM who have received 1–3 prior lines of therapy and in the European Union for patients with MM who have received at least 1 prior therapy.[14]

Preclinical studies suggested that isatuximab targets tumor cells through a combination of mechanisms; namely, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[14] In addition, isatuximab provokes direct apoptosis, without cross-linking agents or immune effector cells, and can induce myeloma-specific antitumor immunity in responding patients.[15,16]

Clinical studies demonstrated the anti-MM activity of isatuximab and the benefit of combining it with conventional immunomodulatory drugs. In a phase I dose-escalation/expansion study, isatuximab monotherapy demonstrated a manageable safety profile and clinical activity in patients with RRMM. Doses from 0.0001 to 20 mg/kg were examined, and the maximal tolerated dose was not reached, with no observed cumulative adverse reactions. The overall response rate (ORR) was 23.8% for patients receiving isatuximab ≥10 mg/kg.[17] Isatuximab was also tested in

combination with lenalidomide and dexamethasone (Rd) or Pd. In a phase Ib dose-escalation study, isatuximab was evaluated, under different dosing regimens, in combination with Rd in heavily pretreated patients with RRMM (≥3 prior treatment lines). The combination proved to be active and well-tolerated. The ORR was 56% and comparable between isatuximab 10 mg/kg Q2W and isatuximab 10 or 20 mg/kg given weekly for 4 weeks, then Q2W thereafter (QW4-Q2W).[18] In a parallel phase Ib dose-escalation study, isatuximab combined with Pd showed clinical activity (ORR of 62%) and a manageable safety profile in heavily pretreated patients with RRMM.[19]

In MM, progression-free survival (PFS) and overall survival end points usually take longer to mature, and these data from phase I and phase I/II clinical trials can not be used to support early decision making. Thus, modeling longitudinal dynamics of M-protein, as a tumor burden marker, in patients with MM may represent an alternative approach to support dosing rationale in the early clinical development steps. This analysis describes the mathematical pharmacokinetic/pharmacodynamic (PK/PD) modeling of serum M-protein based on the framework initially developed by Thai et al.,[20,21] to guide dose selection of isatuximab alongside its clinical program.

MATERIALS AND METHODS

Clinical studies and treatments

Patient PK (isatuximab concentrations) and PD (serum M-protein concentrations) data were collected from multiple clinical studies, including a phase I-II/stage one study of monotherapy isatuximab,[17] a phase Ib study of isatuximab in combination with Rd (Isa-Rd),[18] and a phase Ib study in combination with Pd (Isa-Pd).[19] The detailed dose regimens are presented in Supplementary Material (Patient data) and Table S1. Evaluable patients for the PK/PD analysis were those who were diagnosed using serum M-protein criteria and had two serum M-protein values, with at least one value on isatuximab treatment. The PK/PD monotherapy population included 122 patients, accounting for 774 serum M-protein observations. For the PK/PD analysis of isatuximab in combination with lenalidomide, data from the monotherapy (n = 122) and the Isa-Rd (n = 40) studies were pooled, resulting in 1295 serum M-protein concentration time points. Similarly, data from the monotherapy (n = 122) and the Isa-Pd (n = 31) studies were pooled, accounting for 1168 serum M-protein concentration time points.

All studies were conducted according to the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines. The protocol was approved by institutional review boards and independent ethics committees at all participating institutions. All patients provided written informed consent.

Data measurement

Plasma concentration of functional isatuximab was measured in all clinical studies using a validated enzyme-linked immunosorbent assay with a lower limit of quantification (LLOQ) of 0.5 ng/ml. To measure plasma concentrations of lenalidomide and pomalidomide, a validated high-performance liquid chromatography with tandem mass spectrometry method was applied, with an LLOQ of 5 ng/ml for lenalidomide and 0.2 ng/ml for pomalidomide. Serum M-protein was assessed by serum protein electrophoresis and immunofixation electrophoresis. No LLOQ could be provided for serum M-protein measurement because M-protein and its structure is specific for each patient. The actual lowest value for serum M-protein in the three studies was 0.06 g/L.

Model development

Data from each clinical study were collected at predefined cutoff dates. Therefore, the PK/PD analyses were performed separately, depending on data availability and clinical program advancement. Three separate population PK/PD analyses were conducted. The primary PK/PD analysis was initiated using monotherapy study data,[20] followed by analysis of data collected from the combination studies with Rd and then with Pd.

For each analysis, the PK/PD model parameters were sequentially estimated.[22] First, estimated individual PK parameters were obtained from population PK analyses conducted for each study and were used as regressors in the PK/PD model to fit M-protein concentrations and estimate the PD parameters. The individual PK profiles were therefore considered as fixed inputs in the PK/PD model.

Model parameters, except those assumed to lack interindividual variability or fixed ones, followed a log-normal distribution: $\psi_{i(k)} = \mu_{(k)} e^{\eta_{i(k)}}$, where $\eta_{i(k)} \rightarrow N\left(0, \omega^2_{(k)}\right)$. In the latter formula, $\psi_{i(k)}$ is an individual parameter; $\mu_{(k)}$ the population parameter (fixed effect); $\eta_{i(k)}$ a random effect, and $\omega^2_{(k)}$ its variance. Unless otherwise specified, a combined residual error model was used to fit the data.

All PK and PK/PD analyses were performed using the software Monolix (version 2016R1; Antony, France: Lixoft SAS). Parameters were estimated in a nonlinear mixed-effects approach using stochastic approximation of the expectation-maximization method implemented in Monolix. Data were processed in the software SAS (version 9.3; Cary, NC, USA) and figures were created in the software R (version 3.6.1, 2019–07–05).

PK models

Briefly, the isatuximab PK model is a two-compartment model with linear and nonlinear elimination from the central compartment. To account for target-mediated drug disposition, the nonlinear elimination was approximated by a saturable process described by the Michaelis-Menten equation.[23] The model is given by the following ordinary differential equation system:

$$\frac{dA_c}{dt} = -k_{12} * A_c + k_{21}A_p - k_{10} * A_c - \frac{V_m}{K_m + \frac{A_c}{V_c}} * A_c + In(t), \quad (1)$$

$$\frac{dA_p}{dt} = k_{12} * A_c - k_{21}A_p, \quad (2)$$

where Ac is the amount of drug in the central compartment and Ap the amount in the peripheral one. Parameters $k_{10}\left(=\frac{C_L}{V_1}\right)$ is the first-order rate constant related to the linear elimination, and $k_{12}\left(=\frac{Q}{V_1}\right)$ and $k_{21}\left(=\frac{Q}{V_2}\right)$ are the first-order rate constants between central and peripheral compartments. The constant V_c is the volume of distribution in the central compartment. V_m and K_m are Michaelis-Menten parameters related to nonlinear elimination, with Km representing the drug concentration value at which the elimination rate is half the maximum (Vm). The function $In(t)$ is the infusion rate.

For lenalidomide, concentration data collected from the Isa-Rd study (52 patients, 381 observed concentrations) were enough to estimate population model parameters by using the one-compartment model developed by Dahut et al.[24] To evaluate our results, our estimated model parameters were compared with those obtained by Dahut et al. For pomalidomide, concentrations data collected from the Isa-Pd study were not sufficient to develop a population PK model (45 patients, 441 observed concentrations), thus the two-compartment PK model developed by Li et al.[25] was used to estimate data from the Isa-Pd population. First, pomalidomide PK profile simulations, using the Li et al. model, confirmed the model's ability to describe the data optimally. Then, a posterior Bayesian analysis was performed to estimate individual pomalidomide PK parameters and the geometrical means were compared with the population PK parameters reported by Li et al.

Tumor growth inhibition model

Although the efficacy response assessment in MM is a composite of laboratory tests (M-protein [serum or urine]), imaging, and bone-marrow plasma cell percentage (for patients with a complete response); evolution of measurable M-protein is the most important determinant of tumor response and progression according to the IMWG.[26] The longitudinal serum M-protein variations were characterized using a tumor growth inhibition (TGI) model developed by Claret et al.[27,28] with serum M-protein as a surrogate for tumor growth. The model accounted for tumor growth dynamics, represented by M-protein levels, antitumor drug effect, and resistance to drugs over time (Equation 3). In the absence of treatment, serum M-protein kinetics follows an exponential growth without any saturation and is described by a first-order rate constant (K_L), which stands for serum M-protein proliferation. Drug effect was tested as inhibition of serum M-protein proliferation (K_L) or stimulation of serum M-protein elimination (K_D) considering each drug's mechanism of action.

Multiple concentration-effect link functions were examined; namely Power, Emax, Sigmoidal Emax, and linear functions. Standard goodness-of-fit plots (i.e., predictions vs. observations, residual plots, and visual predictive checks [VPC]), and the Bayesian Information Criteria (BIC) qualified model performance. Model selection was based on the model giving the lowest BIC and low uncertainty on parameter estimates (RSE ≤30% for fixed-effect parameters and ≤50% for random-effect parameters). Additionally, to account for increased patient dropout rates as time under treatment increased, a hazard model (Equation 4) that depends on time and M-protein levels was added into the model. The model is described by the following differential equations:

$$\begin{aligned} \frac{dM}{dt} &= K_L * M - K_D * e^{-R*t} * \left(\frac{A_c}{V_c} + k * C_{\text{len or pom}}\right) * M; \\ M(t=0) &= M0 \end{aligned} \quad (3)$$

$$\lambda(t, M) = \lambda_0 * e^{\beta_T * \log(t) + \beta_M * M}, \quad (4)$$

where $M(t)$ represents serum M-protein concentration at time t, K_L the tumor growth rate, K_d the drug-constant killing rate, and k the coefficient for a combination drug.

The function e^{-R*t} diminishes drug potency over time due to emergent resistance. For monotherapy isatuximab, $k = 0$. For combination studies, it was assumed that the killing rate is linearly and additively proportional to the drug concentration $\left(\frac{A_c}{V_c} + k * C_{\text{len or pom}}\right)$, with $C_{\text{len or pom}}$ being the concentration of either lenalidomide or pomalidomide. Subsequently, concentrations were converted to molar units (isatuximab, 150,000 Da; pomalidomide, 273.24 Da; and lenalidomide, 259.261 Da). The hazard model assumes that a patient's probability to drop out from the trial increases with time and if their tumor load increases. Consequently, the constant β_M relates to the tumor load (M) explanatory variable and the constants λ_0 and β_T adjust the shape of the baseline hazard function $\lambda_0 t^{\beta_T}$.

Simulations to investigate dose regimen efficacy

Individual M-protein profiles were simulated (using Empirical Bayes Estimates from PK/PD model) for isatuximab monotherapy and combined with Rd or Pd. Consequently, the number of simulated profiles equaled the number of patients enrolled in each study. For isatuximab monotherapy, serum M-protein profiles were simulated under the following dose regimens: 3, 5, 10, and 20 mg/kg Q2W; 5, 10, and 20 mg/kg QW4-Q2W. The effect of extending the weekly loading-dose period up to 4, 6, or 8 weeks at 20 mg/kg (QW4-Q2W, QW6-Q2W, or QW8-Q2W) was also simulated. For the Rd or Pd combinations, the same dose regimens for isatuximab as simulations of monotherapy were simulated in combination with 25 mg or 10 mg of lenalidomide according to protocol criteria, or 4 mg of pomalidomide, once daily from day 1 to 21 in a 28-day cycle. Median (with 5th and 95th percentiles) change from baseline serum M-protein levels and percentage of patients achieving 50% and 90% (defined as simulated response rate [SRR]) of serum M-protein reduction were evaluated at weeks 8 and 12. Dosing regimens were compared according to simulated serum M-protein reduction.

RESULTS

Patients

Patient characteristics and dosing schedules from the three studies are presented in Table 1 and Table S1. Patient characteristics between studies were similar except for the MM International Staging System (ISS) category. In the Isa-Pd study, 90% of patients were classified ISS 1–2, whereas patients from other studies were evenly classified ISS from 1 to 3, including more advanced disease.

TABLE 1 Patient characteristics

		Monotherapy		Isa-Rd		Isa-Pd	
Study		***n* = 122**		***n* = 40**		***n* = 31**	
Weight (kg)	Mean (SD)	78.2 (20.9)		75.5 (19.2)		82.4 (18.9)	
	Median (min: max)	74.45 (41.2: 151.8)		72.9 (37.7: 127.3)		83.5 (49.6: 120.8)	
Body surface area*1 (m²)	Mean (SD)	1.90 (0.29)		1.86 (0.27)		1.94 (0.27)	
	Median (min: max)	1.88 (1.30: 2.83)		1.85 (1.24: 2.51)		2.01 (1.48: 2.34)	
Age (years)	Mean (SD)	62.8 (8.7)		61.2 (7.5)		66.3 (8.5)	
	Median (min: max)	64 (38: 81)		61.5 (45: 76)		66 (42: 82)	
Categorical data		***N***	**%**	***N***	**%**	***N***	**%**
Age	<65 years	67	54.9	25	62.5	13	41.9
	≥65–75 years	48	39.3	14	35.0	14	45.2
	≥75 years	7	5.7	1	2.5	4	12.9
Race	White	99	81.1	32	80.0	28	90.3
	Black	8	6.6	5	12.5	1	3.2
	Oriental*2	3	2.5	2	5.0	1	3.2
	Hispanic	1	0.8	1	2.5	–	–
	Other	11	9.0	0	0.0	1	3.2
Gender	Male	69	56.6	19	47.5	17	54.8
	Female	53	43.4	21	52.5	14	45.2
Prior line of therapy	<5	53	43.4	7	17.5	20	64.5
	≥5	69	56.6	33	82.5	11	35.5
ISS*3	1	42	34.4	11	27.5	15	48.4
	2	41	33.6	8	20.0	13	41.9
	3	37	30.3	15	37.5	2	6.5

Body surface area *1: monotherapy $n = 119$, Comb. Pd $n = 27$, Race *2: Asian/Oriental for Comb. Pd.

ISS*3: International Staging System for multiple myeloma, monotherapy $n = 120$, Isa-Rd $n = 34$, Isa-Pd $n = 30$.

Abbreviations: Isa-Pd, isatuximab in combination with pomalidomide and dexamethasone; Isa-Rd, isatuximab in combination with lenalidomide and dexamethasone; ISS, International Staging System.

Pharmacokinetics of isatuximab, lenalidomide, and pomalidomide

Isatuximab PK models from the three separate studies are presented in Table 2. The parallel linear and Michaelis-Menten elimination model adequately fitted isatuximab concentration data for both monotherapy and combination studies (Figure S1). All PK parameters in each model were comparable and well-estimated with low uncertainty (RSE ≤26%). In addition, exposure parameters for isatuximab were derived and compared (data not shown), confirming that the PK of isatuximab in combination with Rd or Pd was similar to the PK of single-agent isatuximab.[17,18]

For lenalidomide, the estimated population PK parameters were comparable to those reported in the literature in single-agent settings (Table S2).[24]

For pomalidomide, population PK parameters were extracted from the Li et al. study.[25] Pomalidomide observed concentrations were mostly included in the 90% prediction interval simulated with the Li's model (Figure S2). The Bayesian analysis using dosing histories and observed concentrations from the Isa-Pd study revealed that the geometric means of the individual PK parameters were comparable to population parameters obtained by Li et al. (Table S3). An additional comparison based on noncompartmental PK analysis with other published data in patients with MM treated with pomalidomide as single agent demonstrated plasma exposure parameters comparable with our study (Table S4).

Overall, the above PK analyses suggested no mutual PK interaction between isatuximab in combination with either lenalidomide or pomalidomide.

Tumor growth inhibition model

The median number and range of serum M-protein observations/patient were 6.34 (2–29), 13.0 (3–38), and 12 (3–25) for monotherapy, Isa-Rd, and Isa-Pd separate analyses, respectively.

Serum M-protein longitudinal models for the three studies, with data from monotherapy studies alone or pooled data monotherapy and each combination study, are presented in Table 3. For the isatuximab monotherapy studies, the longitudinal serum M-protein concentrations were best fitted by a TGI model with isatuximab concentration linearly stimulating serum M-protein elimination. Simulations based on individual predicted model parameters illustrated a good description of M-protein over time by the model (Figures S4 and S5). All model parameters were estimated with low uncertainty (6% ≤ RSE ≤41%).

For the Isa-Rd study, the longitudinal serum M-protein concentrations were best fit by applying a function that linearly stimulates the serum M-protein elimination and is

TABLE 2 Pharmacokinetics parameters of isatuximab

	Study data					
	Monotherapy		Isa-Rd		Isa-Pd	
Parameter	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	RSE (%)
$C_L(L \cdot h^{-1})$	0.00753	9	0.00686	16	0.00798	11
$V_1\,(L)$	4.85	3	4.82	5	5.23	5
$Q(L \cdot h^{-1})$	0.0418	10	0.0454	11	0.0605	11
$V_2\,(L)$	5.68	8	5.89	10	6.55	11
$V_m\,(\mathrm{mg \cdot h \cdot L^{-1}})$	0.146	7	0.118	14	0.0845	26
$K_m\,(\mu\mathrm{g \cdot mL^{-1}})$	0.046	14	0.0415	18	0.046 (FIXED)	N/A
Interpatient variability						
ω_{C_L}	0.939	7	0.953	12	0.572	13
ω_{V_1}	0.321	6	0.367	11	0.281	14
ω_Q	0.798	11	0.607	16	0.391	28
ω_{V_2}	0.780	8	0.692	13	0.656	16
ω_{V_m}	0.638	9	0.702	14	0.877	21
ω_{K_m}	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: Isa-Rd, isatuximab combined with lenalidomide and dexamethasone; Isa-Pd, isatuximab combined with pomalidomide and dexamethasone; RSE, relative standard error; C_L, clearance, V_1, central volume of distribution; Q, intercompartment clearance, V_2, peripheral volume of distribution; V_m,K_m, Michaelis-Menten rate constants; ω, standard deviation; N/A, not applicable.

TABLE 3 Tumor growth model parameters

	Study data					
	Monotherapy		Isa-Rd		Isa-Pd	
Parameter	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	RSE (%)
$M_0\ (g \cdot L^{-1})$	24.4	6	23.8	5	21.4	6
$K_L\ (d^{-1})$	0.00407	15	0.00364	12	0.00312	14
$K_D\ (mol^{-1} \cdot d^{-1})$	0.0182	27	0.0193	17	0.0125	21
$R(d^{-1})$	0.0198	28	0.0175	15	0.0169	13
K	N/A	N/A	2.69	14	34.6	13
λ_0	0.0000273	41	0.0000255	N/A	0.0000116	21
β_T	0.85	8	0.803	3	0.977	3
β_M	0.0476	8	0.0528	5	0.0539	6
Interpatient variability						
ω_{M_0}	0.654	7	0.655	6	0.694	6
ω_{K_L}	1.05	52	1.18	8	1.28	8
ω_{K_D}	1.54	12	1.49	9	1.55	11
ω_R	1.23	15	1.17	12	0.886	13
k	N/A	N/A	0.631	23	0.361	33
ω_{λ_0}	–	N/A	–	N/A	–	N/A
ω_{β_T}	–	N/A	–	N/A	–	N/A
ω_{β_M}	–	N/A	–	N/A	–	N/A
Residual error						
Additive (g/L)	0.927	14	0.549	11	0.55	8
Proportional	0.0607	15	0.0958	8	0.0979	7

Abbreviations: Isa-Rd, isatuximab combined with lenalidomide and dexamethasone; Isa-Pd, isatuximab combined with pomalidomide and dexamethasone; RSE, relative standard error;M_0, baseline tumor value; K_L, tumor growth rate; K_D, cell kill rate (converted to molar for combination studies); R, resistance appearance; k, ratio effect of lenalidomide over isatuximab or of pomalidomide over isatuximab; λ_0, baseline hazard coefficient; β_T, β_M, hazard function coefficients; ω, standard deviation; N/A, not applicable.

additively proportional to the concentration of each drug (Equation 3). The population PK/PD analysis yielded parameter estimates with low uncertainty (3% ≤ RSE ≤23%) for both fixed and random effects (Table 3).

For the Isa-Pd study, the longitudinal serum M-protein model also yielded parameter estimates with low uncertainty (3% ≤ RSE ≤33%) for both fixed and random effects (Table 3). Parameter estimates were comparable to those obtained for monotherapy, except for the baseline serum M-protein level. Overall, model parameters were consistent among the three studies and standard diagnostic plots were acceptable (Figures S4 and S5–S7). VPC of the survival function also illustrated that dropout time was well-described by the dropout model for the three analyses (Figure S8).

Simulations

For isatuximab monotherapy, individual simulated profiles revealed a dose-effect relationship with the greatest serum M-protein reduction occurring at the highest dose of 20 mg/kg QW4–Q2W. The median percentages of change from baseline of serum M-protein at weeks 8 and 12 were −52.1% and −60.6 at 20 mg/kg QW4–Q2W, whereas the corresponding reductions were −17.9% and −20.9%, respectively, for 10 mg/kg QW4–Q2W. Doses below 10 mg/kg did not reduce serum M-protein levels (Table 4). The SRR (percentage of patients achieving ≥50% M-protein reduction from baseline) at week 8 for dose regimens 3, 5, 10, and 20 mg/kg Q2W were 0.8%, 1.6%, 11.5%, and 25.4%, respectively, whereas they were 6.6%, 20.5%, and 40.2% for the 5, 10, and 20 mg/kg QW4–Q2W dose regimen, respectively (Table 5). For dosing regimens with a prolonged weekly loading period, the median percentages of change in serum M-protein from baseline at week 8 of QW4–Q2W, QW6–Q2W, and QW8–Q2W were −52.1, −56.7, and −58.3, respectively. These simulations revealed that isatuximab 20 mg/kg QW4–Q2W decreased serum M-protein levels appropriately and extending the loading period beyond 4 weeks does not improve M-protein reduction.

TABLE 4 Model predicted response rates for monotherapy isatuximab and combination therapy with lenalidomide or pomalidomide under different dose regimens

Study		Monotherapy ($n = 122$)		Isa-Rd ($n = 40$)		Isa-Pd ($n = 31$)	
Dose	Time (weeks)	*N*	% change of M-protein	*N*	% change of M-protein	*N*	% change of M-protein
3 mg/kg Q2W	8	91	24.1 (−8.9:139.8)	35	−24.58 (−100:29.63)	30	−64.27 (−98.09:46.84)
	12	73	38.9 (−27.1:266.5)	33	−28.17 (−100:102.64)	28	−75.84 (−99.01:9.39)
5 mg/kg Q2W	8	88	14.9 (−33.4:134.9)	36	−31.8 (−100:17.79)	30	−66.75 (−98.4:43.78)
	12	76	28.8 (−45.7:251)	33	−40.36 (−100:15.74)	28	−78.16 (−99.22:8.83)
10 mg/kg Q2W	8	91	1.3 (−84.1:123.5)	37	−55.26 (−100:3.42)	30	−72.66 (−99.1:31.01)
	12	77	−4 (−97.2:192.4)	33	−68.44 (−100:2.68)	28	−83.93 (−99.65:6.89)
20 mg/kg Q2W	8	94	−30.5 (−99:74.7)	37	−80.95 (−100:−6.25)	31	−81.46 (−99.72:4.67)
	12	80	−38.4 (−99.9:107.5)	33	−90.44 (−100:−23.66)	29	−90.76 (−99.93:81.64)
5 mg/kg QW4-Q2W	8	90	7.2 (−72.8:129.5)	36	−48.1 (−100:5.8)	30	−70.3 (−98.87:39.63)
	12	77	10.4 (−84.5:220.1)	33	−55.7 (−100:13.46)	28	−81.1 (−99.48:7.84)
10 mg/kg QW4-Q2W	8	96	−17.9 (−96.7:93.1)	37	−72.9 (−100:−2.34)	30	−79.1 (−99.56:−0.98)
	12	80	−20.9 (−99.3:153.2)	33	−82.3 (−100:−11.45)	29	−87.7 (−99.85:136.56)
20 mg/kg QW4-Q2W	8	94	−52.1 (−100:36.4)	37	−93.6 (−100:−16.41)	31	−87.9 (−99.93:−4.74)
	12	82	−60.6 (−100:45.5)	35	−97 (−100:−33.38)	29	−94.5 (−99.99:4.2)

Investigation of loading dose for monotherapy ($n = 122$)							
% change of M-protein	*N*	20 mg/kg QW4-Q2W	*N*	20 mg/kg QW6-Q2W	*N*	20 mg/kg QW8-Q2W
Week 8	94	−52.1 (−100, 36.4)	94	−56.7 (−100, 33.2)	94	−58.3 (−100, 32.0)
Week 12	82	−60.6 (−100, 45.5)	82	−67.2 (−100, 35.3)	83	−70.2 (−100, 30.0)

Abbreviations: Isa-Pd, isatuximab combined with pomalidomide and dexamethasone; Isa-Rd, isatuximab combined with lenalidomide and dexamethasone; *N*, number of patients at 8 and 12 weeks.

Percentage change of M-protein from baseline, median (min: max).

For Isa-Rd, simulations demonstrated a dose-effect relationship with the greatest M-protein reduction occurring for doses greater than or equal to 10 mg/kg. Furthermore, the simulations of regimens with weekly doses for the first cycle (QW4–Q2W) showed a deeper reduction in M-protein levels at weeks 8 and 12, compared with the Q2W regimen (Tables 4 and 5). The median percent change of serum M-protein reduction from baseline at weeks 8 and 12 was −72.9% and −82.3%, respectively, for 10 mg/kg QW4–Q2W, and −93.6% and −97%, respectively, for 20 mg/kg QW4–Q2W. The 90% SRR at week 8 reached 32.5% for the 10 mg/kg QW4–Q2W dose regimen and 50.0% for 20 mg/kg QW4–Q2W (Tables 4 and 5). These simulations demonstrated the benefit of starting with a loading period for isatuximab (QW4–Q2W) compared with Q2W administrations, and confirmed better efficacy with isatuximab ≥10 mg/kg.

For Isa-Pd, all dose regimens revealed a rapid and sustained decrease in serum M-protein concentrations with no apparent dose-effect relationship (Tables 4 and 5). Isatuximab ≥10 mg/kg doses proved to mildly induce greater reduction of serum M-protein levels compared with doses less than 10 mg/kg (i.e., 5 mg/kg), with limited change between the 10 and 20 mg/kg doses.

DISCUSSION

This analysis presented the PK/PD modeling framework that optimized the selection process for an isatuximab dosing regimen in patients with RRMM at an early stage of clinical development by gathering all available information from phase I studies. In all clinical phase I studies, isatuximab was well-tolerated and no clear dose-response was observed between the two highest doses tested (i.e., 10 and 20 mg/kg), therefore making the choice of an appropriate dose level difficult. Moreover, at the time of the analyses, survival data were not mature and could not be used to support early decision making. As an alternative approach, longitudinal M-protein modeling was therefore implemented alongside the clinical studies to support selection of an optimal dosing regimen.

Compared to classical exposure-response (E-R) analyses, this longitudinal analysis of serum M-protein allowed an assessment of the benefits of changing dosing regimens over

TABLE 5 Model predicted response of 50% of M-protein reduction under different dose regimens by study

		Patients with 50% of M-protein reduction						Patients with 90% of M-protein reduction					
		Monotherapy ($n = 122$)		Isa-Rd ($n = 40$)		Isa-Pd ($n = 31$)		Monotherapy ($n = 122$)		Isa-Rd ($n = 40$)		Isa-Pd ($n = 31$)	
Dose	**Time (weeks)**	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
3 mg/kg Q2W	8	1	0.8	11	27.5	20	64.5	0	0	5	12.5	6	19.4
	12	2	1.6	10	25	19	61.3	0	0	4	10	7	22.6
5 mg/kg Q2W	8	2	1.6	13	32.5	20	64.5	1	0.8	5	12.5	6	19.4
	12	2	1.6	14	35	20	64.5	2	1.6	4	10	8	25.8
10 mg/kg Q2W	8	14	11.5	19	47.5	21	67.7	3	2.5	6	4.9	8	25.8
	12	17	13.9	19	47.5	20	64.5	4	3.3	10	25	8	25.8
20 mg/kg Q2W	8	31	25.4	25	62.5	22	71	15	12.3	15	37.5	8	25.8
	12	35	28.7	27	67.5	24	77.4	16	13.1	17	42.5	16	51.6
5 mg/kg QW4-Q2W	8	8	6.6	18	45	20	64.5	3	2.5	5	12.5	7	22.6
	12	8	6.6	18	45	20	64.5	3	2.5	6	15	8	25.8
10 mg/kg QW4-Q2W	8	25	20.5	22	55	21	67.7	9	7.4	13	32.5	8	25.8
	12	26	21.3	24	60	22	71	13	10.7	15	37.5	10	32.3
20 mg/kg QW4-Q2W	8	49	40.2	30	75	24	77.4	21	17.2	20	50	11	35.5
	12	46	37.7	29	72.5	25	80.6	23	18.9	20	50	18	58.1

Investigation of loading dose for monotherapy ($n = 122$)				
% of patients with 50% reduction		**20 mg/kg QW4-Q2W**	**20 mg/kg QW6-Q2W**	**20 mg/kg QW8-Q2W**
Week 8	*N*	49	51	52
	%	40.2	41.8	42.6
Week 12	*N*	46	49	50
	%	37.7	40.2	41

Abbreviations: Isa-Rd, isatuximab combined with lenalidomide and dexamethasone; Isa-Pd, isatuximab combined with pomalidomide and dexamethasone; N, number of patients with 50% of M-protein reduction at 8 and 12 weeks.

time and enabled simulation of dosing schedules not tested in clinical studies. M-protein is a quantitative variable and its easy and straightforward measurement makes it a PD marker of choice. Therefore, the longitudinal PK/M-protein modeling including a dropout model was an appropriate alternative to compare the benefit of different dosing regimens. Longitudinal serum M-protein concentrations were best fitted by a TGI model with isatuximab concentration linearly stimulating serum M-protein elimination. A very similar serum M-protein growth-inhibition model in patients with MM treated with single-agent carfilzomib was published by Jonsson et al.[28] Because PK data were not collected in all patients in the Jonsson's study, the TGI model used full dosing history rather than PK data as the exposure metric to drive drug effect, therefore preventing to understand the contribution of PK variability to patients' response in longitudinal M-protein dynamics. Nevertheless, the M-protein growth rate estimated in the Jonsson's study ($K_L = 0.00404$ day^{-1}) is very close to those estimated by the PK/PD models in isatuximab studies (K_L ranging from 0.00312 to 0.00407 day^{-1}). This finding indicates that this disease-specific parameter in the TGI model for MM is robust and treatment independent. As for carfilzomib, a resistance component was included in the isatuximab TGI models using an exponential function over time $\left(e^{-R*t}\right)$. The resistant terms were estimated with good precision and showed similar values in all three PK/PD models (Table 3). For all models, removing the resistance term degraded the overall fitting (data not shown). This resistance pattern was well-illustrated in several cases of patients showing a rebound of M-protein during treatment (Figure S4). Altogether, the above findings justified the inclusion of a resistance parameter in the TGI model. Noteworthy, the resistance parameter, which is also expected to be a disease-specific parameter, showed comparable values between the carfilzomib ($R = 0.0153$ day^{-1}) and isatuximab models (R ranging from 0.0169 to 0.0198 day^{-1}).

The current semimechanistic model was successfully applied and produced reliable predictions, which were confirmed clinically. For isatuximab monotherapy, simulations showed that reductions in M-protein levels were achieved with doses greater than 10 mg/kg and with regimens including 4 weekly administrations in the first cycle. Furthermore, the model predicted a benefit of increasing the dose from 10 to 20 mg/kg as M-protein levels are reduced by approximately three-fold (Figures 1 and 2). This finding agrees with the 80% receptor occupancy observed with the dose regimen 20 mg/kg QW4–Q2W.[17] Additionally, the simulations revealed that extending the isatuximab loading period to 6 or 8 weeks would not substantially improve serum M-protein reduction. Consequently, model predictions along with clinical findings and E-R analysis[21] selected isatuximab 20 mg/kg QW4–Q2W as monotherapy for patients with RRMM. The 20-mg/kg dosing regimen was assessed in the phase I/II ISLAND study in Japanese patients with RRMM, whose results demonstrated a 36.4% ORR (12/33 patients).[29]

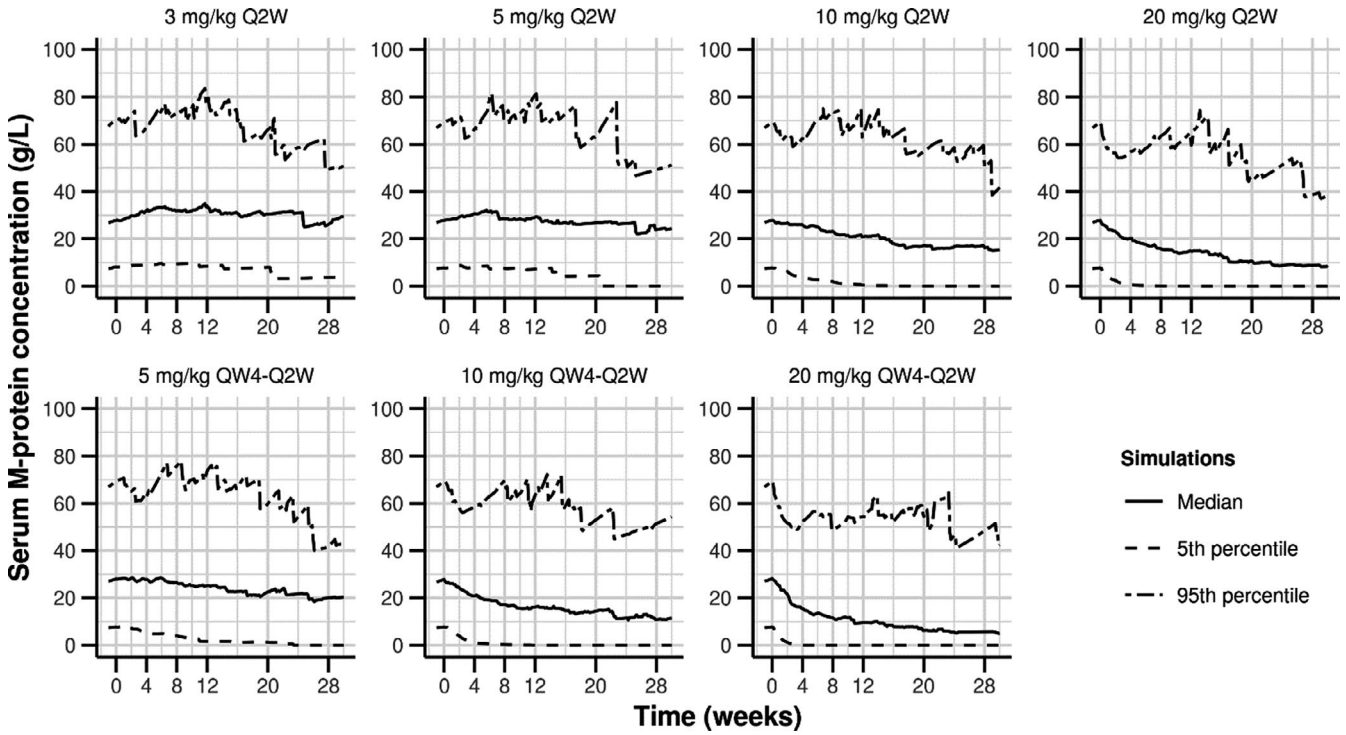

FIGURE 1 Model predictions of M-protein profiles under different isatuximab dose regimens. Q2W, administration every 2 weeks; QW4-Q2W, weekly administration for 4 weeks followed by every 2 weeks thereafter

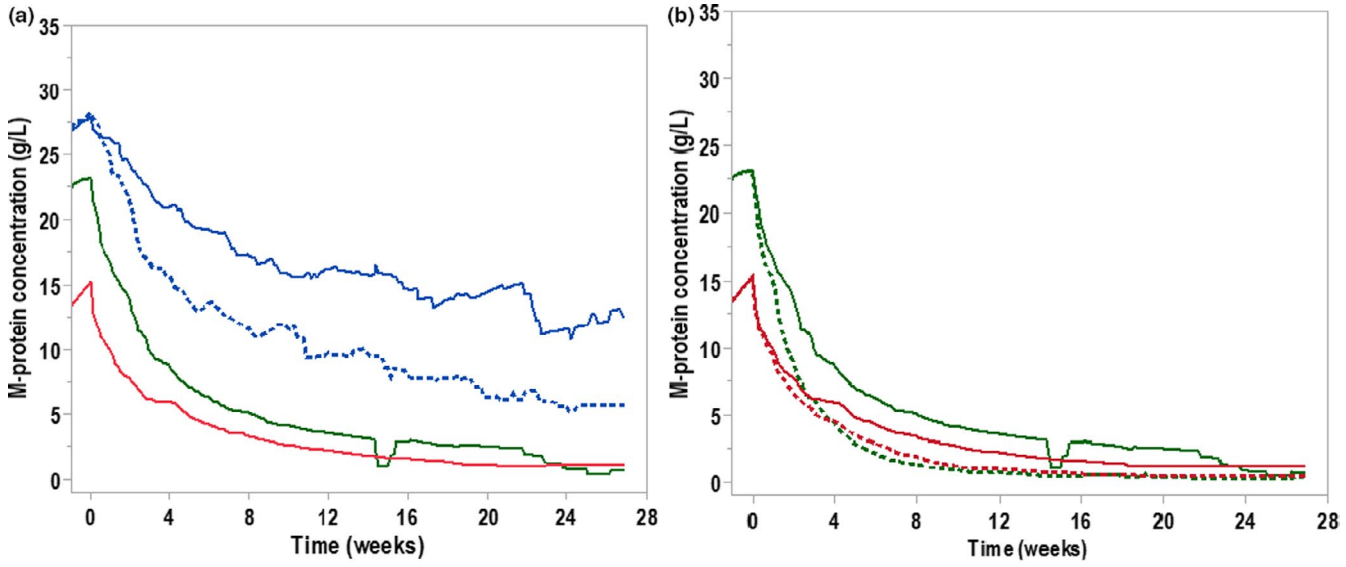

FIGURE 2 Model predictions of M-protein profiles under different isatuximab dose regimens in mono- and combination therapy. (a) Comparison of median predicted serum-M protein concentrations between isatuximab monotherapy (10 and 20 mg/kg QW4–Q2W) and each combination therapy isatuximab 10 mg/kg QW4–Q2W with lenalidomide or pomalidomide. (b) Comparison of median predicted serum M-protein concentrations between isatuximab 10 mg/kg QW4–Q2W and 20 mg/kg QW4–Q2W on each combination with lenalidomide or pomalidomide. d, dexamethasone; P, pomalidomide; Q2W, administration every 2 weeks; QW4-Q2W, weekly administration for 4 weeks followed by every 2 weeks thereafter; R, lenalidomide

For Isa-Rd, model predictions confirmed, similar to the monotherapy study, that regimens initiated with weekly dosing for cycle 1 (QW4–Q2W) induced a greater reduction in M-protein levels compared with Q2W dosing. However, simulations revealed that increasing the isatuximab dose from 10 to 20 mg/kg does not significantly affect M-protein reduction (Figure 2). Moreover, serum M-protein reduction was greater when isatuximab was given in combination at 10 mg/kg QW4–Q2W compared with single-agent administration at 10 or 20 mg/kg QW4–Q2W (Figure 2). Compared with the threefold change between 10 and 20 mg/kg QW4–Q2W in monotherapy study, simulations illustrated a no more than 1.3-fold difference between these two dose regimens. This limited impact of higher isatuximab doses on efficacy could be explained by the potency of the combination with lenalidomide. For Isa-Pd, the model did not predict a dose-effect relationship on M-protein reduction. This may be due to data imbalance in the Pd-combination study, in which most of the patients were treated at 10 mg/kg QW4–Q2W ($n = 23$). Few patients received other doses; four patients received 5 mg/kg QW4–Q2W and four received 20 mg/kg QW4–Q2W. Although the scarce data in the Isa-Pd study restrained predictions for low doses, predictions for doses greater than or equal to 10 mg/kg agreed with the results of the Rd-combination study. Namely, median M-protein changes from baseline at weeks 8 and 12 for the 10 mg/kg QW4–Q2W regimen, were −79.1% and −87.7%, respectively, for Isa-Pd, and −72.9% and −82.3%, respectively for Isa-Rd. Intuitively, these results underlined the comparable efficacy profile between the two immunomodulatory drugs lenalidomide and pomalidomide, in two MM clinical studies.[18,19] Likewise, the Isa-Pd model confirmed the minimal benefit in increasing dosing from 10 to 20 mg/kg. Consequently, when combined with immunomodulatory drugs, longitudinal M-protein model predictions did not indicate a substantial advantage of the 20 mg/kg over the 10 mg/kg isatuximab dose, leading to selection of isatuximab 10 mg/kg QW4–Q2W for combination studies.

The current modeling framework was consistent with the clinical findings and was complemented by E-R analyses. These E-R analyses suggested that higher exposure (log C_{trough} at week 4) was associated with increased ORR, supporting selection of 10 mg/kg QW4–Q2W dosing for the phase III Isa-Pd combination study.[30] Recent results of the phase III IKEMA study investigating isatuximab 10 mg/kg QW4–Q2W in combination with carfilzomib/dexamethasone, demonstrated significant PFS prolongation and improvement in depth of response, further confirming the anti-myeloma activity of this dosing regimen.[31]

The PK/PD modeling analyses provided informed decisions alongside the clinical studies for substantiating

the isatuximab 10 mg/kg QW4–Q2W dosing regimen in combination with Pd, for further isatuximab combination clinical studies. Subsequently, this dosing regimen was approved in combination with Pd in various countries.[14] This dosing regimen with some adaptations is being further studied in phase III combination studies with lenalidomide/dexamethasone for high-risk smoldering MM (NCT04270409), and with bortezomib/lenalidomide/dexamethasone (NCT03319667 and NCT03617731) or carfilzomib/lenalidomide/dexamethasone in newly diagnosed MM (NCT04483739).

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CONFLICT OF INTEREST

K.K., R.E.-C., H.-T.T., C.B., J.B.F., C.V.-F., M.-L.R., H.v.d.V., D.S., and L.N. are employees of Sanofi and may hold stock and/or stock options in the company.

AUTHOR CONTRIBUTIONS

K.K., R.E.-C., H.-T.T., C.B., J.-B.F., C.V.-F., H.v.d.V., D.S., and L.N. wrote the manuscript. M.-L.R. and H.v.d.V. designed the research. K.K. and H.-T.T. performed the research. K.K., R.E.-C., C.B., J.-B.F., C.V.-F., D.S., and L.N. analyzed the data.

DATA AVAILABILITY

Qualified researchers can request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report forms, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access are at: https://www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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