Received: 21 July 2021 | Revised: 29 September 2021 | Accepted: 21 October 2021

DOI: 10.1111/bcp.15123

ORIGINAL ARTICLE

# Joint modelling and simulation of M-protein dynamics and progression-free survival for alternative isatuximab dosing with pomalidomide/dexamethasone

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**Funding information**
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**Aims:** Addition of isatuximab (Isa) to pomalidomide/dexamethasone (Pd) significantly improved progression-free survival (PFS) in patients with relapsed/refractory multiple myeloma (RRMM). We aimed to characterize the relationship between serum M-protein kinetics and PFS in the phase 3 ICARIA-MM trial (NCT02990338), and to evaluate an alternative dosing regimen of Isa by simulation.

**Methods:** Data from the ICARIA-MM trial comparing Isa 10 mg/kg weekly for 4 weeks then every 2 weeks (QW-Q2W) in combination with Pd versus Pd in 256 evaluable RRMM patients were used. A joint model of serum M-protein dynamics and PFS was developed. Trial simulations were then performed to evaluate whether efficacy is maintained after switching to a monthly dosing regimen.

**Results:** The model identified instantaneous changes (slope) in serum M-protein as the best on-treatment predictor for PFS and baseline patient characteristics impacting serum M-protein kinetics (albumin and β2-microglobulin on baseline levels, non-IgG type on growth rate) and PFS (presence of plasmacytomas). Trial simulations demonstrated that switching to a monthly Isa regimen at 6 months would shorten median PFS by 2.3 weeks and induce 42.3% patients to progress earlier.

**Conclusions:** Trial simulations supported selection of the approved Isa 10 mg/kg QW-Q2W regimen and showed that switching to a monthly regimen after 6 months may reduce clinical benefit in the overall population. However, patients with good prognostic characteristics and with a stable, very good partial response may switch to a monthly regimen after 6 months without compromising the risk of disease progression. This hypothesis will be tested in a prospective clinical trial.

KEYWORDS
modelling and simulation, monoclonal antibodies, pharmacodynamics

The authors confirm that the principal investigator for this paper is Dr van de Velde and he has direct clinical responsibility for patients.

## 1 | INTRODUCTION

Despite significant therapeutic advances and prolongation in overall survival (OS), multiple myeloma (MM) remains incurable, with many patients relapsing and requiring additional treatment.[1] Isatuximab (Isa) is an immunoglobin G1 (IgG1) monoclonal antibody that targets the CD38 transmembrane glycoprotein. Isa kills MM cells via multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, direct induction of apoptosis without cross-linking and inhibition of CD38 enzymatic activity. In a phase 1b study of patients with relapsed/refractory MM (RRMM), a 10 mg/kg weekly for 4 weeks then every 2 weeks (QW-Q2W) dose of Isa in combination with pomalidomide (P) and low-dose dexamethasone (d) (Isa-Pd) achieved an overall response rate (ORR) of 64.5% and median progression-free survival (PFS) of 17.6 months. These results, combined with exposure-response and disease modelling of tumour burden (serum M-protein), provided the justification for the 10 mg/kg QW-Q2W of Isa-Pd.[2,3] This combination was then assessed in the phase 3 ICARIA-MM study (NCT02990338), which showed that addition of Isa to Pd significantly improved PFS in RRMM patients.[4] Based on this pivotal study, Isa in combination with Pd is approved in multiple countries for RRMM patients with ≥2 prior lines. Furthermore, to date, Isa in combination with carfilzomib/dexamethasone is approved in the United States for relapsed MM patients with 1-3 prior lines, and in the European Union for MM patients with ≥1 prior therapy, based on the phase 3 IKEMA study.[5–7]

Efforts have been made to develop tumour growth inhibition (TGI) models and predict clinical responses, OS or PFS rates in cancer patients from various clinical settings.[8,9] TGI models are used to find early changes in tumour size that would predict OS or PFS. Joint models have emerged as a promising framework for concurrently investigating the relationship between continuous disease progression through longitudinal outcomes such as biomarkers, tumour size and incidence of clinical events such as progression and death. These models provide precise and unbiased estimation of the parameters in an informative censoring context.[10] Mechanistic joint models adequately predicted OS in clinical trials for atezolizumab in urothelial carcinoma, cabazitaxel in metastatic prostate cancer and aflibercept in metastatic colorectal cancer.[11–13]

In most patients, MM is characterized by the secretion of a monoclonal Ig protein (M-protein), which is produced by the abnormal plasma cells. Similar to tumour burden for solid tumours, serum M-protein levels are an important part of the response criteria for MM patients[14] and thus their dynamic change can predict long-term clinical benefit (PFS, OS). Several examples in MM showed that TGI modelling based on longitudinal M-protein can be used to predict OS or PFS.[15–18]

For Isa, the joint modelling framework was used to integrate early drug development results with later-stage clinical data from phase 1-2 monotherapy and combination studies.[2,3,19] Disease progression was initially captured together with serum M-protein dynamics using a joint model and accounting for dropout. Longitudinal serum M-protein modelling provided more insights in patient response over time and supported phase 2 and phase 3 dosing-regimen selection in MM patients.[20] This framework and modelling approach can be extended to account for PFS since PFS is a composite endpoint, which depends not only on serum M-protein but also radiological progression or death. This joint modelling therefore improves the predictive and simulation value of the models in exploring the benefits of a different dosing strategy, eg, switching to a monthly regimen after 6 months to reduce dosing intensification in a context of long treatment duration.

The objectives of this work were therefore to (i) quantitatively evaluate the association between serum M-protein kinetics, baseline covariates and PFS in RRMM patients in both Isa-Pd and Pd arms of the ICARIA-MM study, and (ii) simulate longitudinal serum M-protein and PFS when switching to a hypothetical monthly Isa dosing regimen after 6 months.

### What is already known about this subject

- Addition of isatuximab (Isa) 10 mg/kg weekly for 4 weeks then every 2 weeks (QW-Q2W) to pomalidomide/dexamethasone (Pd) significantly improved progression-free survival (PFS) in patients with relapsed/refractory multiple myeloma (MM) in the phase 3 ICARIA-MM trial.
- Serum M-protein is known as a surrogate marker of tumour burden in MM and can predict long-term clinical benefit such as PFS.

### What this study adds

- Association of M-protein kinetics, patient characteristics and PFS was well characterized by joint modelling.
- The simulation demonstrated that switching to an Isa monthly regimen after 6 months may reduce clinical benefit, supporting FDA-approved Isa QW-Q2W dosing. However, patients with good prognosis may switch to monthly dosing after 6 months without compromising risk of disease progression.

## 2 | METHODS

### 2.1 | Study design and data

Data were obtained from the ICARIA-MM study. Isa was administered intravenously at 10 mg/kg QW for 4 weeks followed by Q2W for 28-day cycles in combination with standard pomalidomide (4 mg orally on days 1-21/each cycle) and dexamethasone (40 or 20 mg for patients aged ≥75 years orally or intravenously on days 1, 8, 15 and 22 in each cycle). The study was conducted following the principles of the Declaration of Helsinki and ICH Good Clinical Pratice (GCP)

Guidelines. The protocol was approved by institutional review boards and independent ethics committees at the participating institutions. All patients provided written informed consent. The primary study endpoint was PFS, defined as the time from randomization to first documentation of progressive disease or death from any cause, whichever came first. Response and disease progression were determined by an independent response committee using the International Myeloma Working Group (IMWG) criteria, based on central, M-protein laboratory assessments and radiology review.[14] Patients with ≥2 serum M-protein values, including one baseline value and for whom response could be evaluated by serum M-protein, were included in the analysis. Serum M-protein was assessed by serum protein electrophoresis and immunofixation electrophoresis.[20] Per protocol, serum M-protein was measured at baseline, end of each cycle, and study end. No lower limit of quantification (LOQ) could be provided for serum M-protein measurement because M-protein and its structure are patient-specific. For this analysis, LOQ was considered as half of the actual lowest value for serum M-protein in the ICARIA-MM study (ie, 0.5 g/L).

## 2.2 | Model development

Serum M-protein longitudinal data from both study arms and PFS data were first modelled separately. To account for dose effect, treatment exposure over time was introduced in the longitudinal model using concentrations predicted by the individual PK parameters for Isa and a kinetic-pharmacodynamic (K-PD) model for pomalidomide and dexamethasone. Several joint models were then used to find the best link between serum M-protein kinetics and PFS.

### 2.2.1 | Population PK model for Isa

A two-compartment PK model with parallel linear and nonlinear (Michaelis-Menten) elimination from the central compartment and time-varying linear clearance function was used to describe the Isa plasma concentrations versus time data collected from 476 MM patients who received 1-20 mg/kg Isa alone or in combination with Pd in four phase 1-3 clinical trials, including ICARIA-MM.[21] The equations of this structural PK model are presented in the Supporting Information. Individual PK parameters for ICARIA-MM patients were obtained as post hoc estimates and typical PK parameters were attributed for patients without PK data.

### 2.2.2 | K-PD model for pomalidomide and dexamethasone

Since concentrations of combined Pd were not measured in this study, the kinetics of these drugs were simplified using a K-PD modelling approach.[22] Their PK was therefore described by a simple, virtual one compartment with bolus input and fixed elimination-rate constant derived from their central distribution volume and clearance value estimates in the literature.[23,24]

### 2.2.3 | TGI model for M-protein data and covariate selection

*Structural model*

A TGI model accounting for tumour growth dynamics, antitumour drug effect and resistance to drug effect was developed by Claret et al.[25] This model was also successfully applied to describe serum M-protein data as a surrogate of tumour growth in MM patients.[15,16,18,26,27] In this analysis, a mechanism-based model drawn from the Claret's TGI model was proposed to describe the underlying disease progression and exposure-driven drug effect of Isa and Pd on the serum M-protein time-course. The structural model for this TGI model, shown in Figure 1, is described by the following differential equation:

$$\frac{dM}{dt} = KL * M - KD_i * e^{-R_i * t} * C_{iM} * M - KD_{pd} * e^{-R_{pd} * t} * (C_{pM} + C_{dM}) * M;$$
$$M(t=0) = M0$$

where $M$ is serum M-protein at time $t$, $\boldsymbol{M0}$ is the baseline serum M-protein, $\boldsymbol{KL}$ is the tumour growth rate, $KD_i$ and $KD_{pd}$ are the shrinkage rate due to Isa and combined Pd exposure respectively, $R_i$ and $R_{pd}$ are the rate constant of resistance appearance to Isa and combined Pd, respectively, and $C_{iM}$, $C_{pM}$ and $C_{dM}$ are the molar concentrations of Isa, pomalidomide and dexamethasone at time $t$, respectively. The contribution of $C_{pM}$ and $C_{dM}$ in increasing M-protein shrinkage rate $KD_{pd}$ was assumed to be equal based on the response rates of a randomized phase 2 study comparing pomalidomide alone or combined with dexamethasone.[28]

*Statistical model*

An exponential interindividual model implying a log-normal distribution was included on all parameters. The variance-covariance matrix was modelled using a diagonal matrix. The residual variability was modelled using a combined additive and proportional model.

*Covariate analysis*

Covariate analysis was performed after obtaining the base model. Twenty-six baseline covariates were tested: demographics, baseline laboratory measurements and disease-related patient characteristics (Supporting Information Table S1). In the case of missing data, the median value was input for continuous covariates; missing was considered as an additional category for categorical covariates. The parameter-covariate relationship was first explored graphically using individual parameter estimates. The Conditional Sampling for Stepwise Approach based on Correlation tests (COSSAC) covariate selection algorithm was then used for automatic building of the covariate model.[29,30] The best covariate model was selected using the corrected version of Bayesian Information Criteria (BICc).[31] Additionally, only

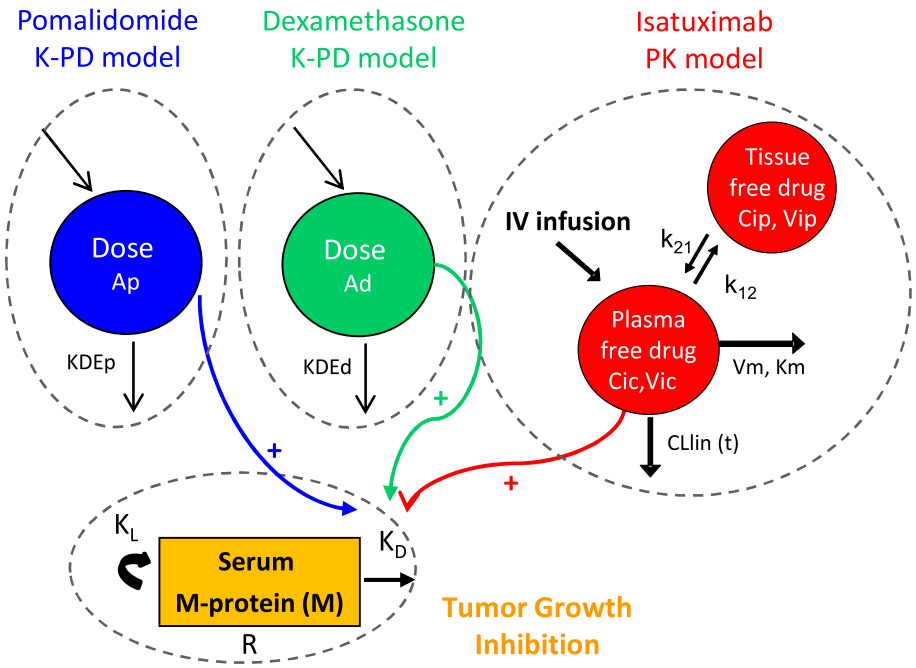


**FIGURE 1** Schematic representation of the integrated drug disease model. It integrates kinetic-pharmacodynamic models (K-PD) for pomalidomide and dexamethasone, the pharmacokinetic (PK) model for isatuximab, and the tumour growth inhibition (TGI) model for serum M-protein

significant covariates with Wald test *P* value <.05 were kept in the final model.

#### 2.2.4 | PFS model and covariate selection

PFS was modelled using a parametric proportional-hazard model with log-logistic distribution for baseline hazard: $h_0(t) = \frac{\frac{s}{Te}\left(\frac{t}{Te}\right)^{s-1}}{1+\left(\frac{t}{Te}\right)^{s}}$ where *Te* is the scale parameter (characteristic time) and *s* the shape parameter. The exponential and Weibull distribution were also tested. The baseline covariates were tested as potential prognostic factors using the classical stepwise covariate modelling method. The same criteria for covariate selection in the longitudinal M-protein model development were used.

### 2.3 | Joint modelling of serum M-protein and PFS

Longitudinal and PFS models were built separately; thereafter several joint models were used to find the best link between serum M-protein kinetics and PFS, relying on the following link functions:

- no link
- current serum M-protein: $M(t)$
- current M-protein slope (instantaneous rate of change in serum M-protein): $dM/dt$
- area under the M-protein.

Significant covariates found in the longitudinal and PFS submodels were evaluated, and only covariates significant with the Wald test (*P* value <.05) were kept in the joint model.

### 2.4 | Parameter estimation

Parameter estimation of all models was performed using the Stochastic Approximation Expectation Maximization (SAEM) algorithm implemented in the software Monolix v.2019R1. Data below LOQ for serum M-protein were accounted for using the extended SAEM algorithm implemented in Monolix.

### 2.5 | Model selection and evaluation

Model selection was based on BIC for non-nested models and the model giving the lowest BICc was retained. The likelihood ratio test was used to discriminate between nested models through the difference in log likehood (−2LL), computed using important sampling. A *P* value of .05 was considered statistically significant. Model evaluation was performed by investigating both residual- and simulation-based diagnostics, including the individual weighted residuals (IWRES), visual predictive checks (VPC) for the longitudinal part, Cox-Snell and deviance residuals,[32] de-trended prediction discrepancies,[33] and Kaplan-Meier VPC for PFS, respectively. Additional goodness-of-fit plots were assessed by visual inspection of individual fits or by comparing observations versus individual predictions. Longitudinal VPC accounted for risk of progression using the methods described by Friberg et al.[34] Briefly, this involved reproducing the event mechanisms in simulation and omitting simulations occurring after a simulated progression time. PFS VPC considered the design of each patient, ie, dose regimens and follow-up duration. Indeed, simulated time to progression (TTP) was censored by the maximum time between duration of follow-up, end of treatment and observed TTP.

### 2.6 | Simulation of monthly dosing regimen

To evaluate longitudinal serum M-protein and PFS after switching to a hypothetical monthly (Q4W) Isa dosing regimen after 6 months, 1000 trials (using the same design and patient characteristics as in the data) were simulated with both the Isa-Pd and Pd arms for 80 weeks. All the drug-related parameters, in particular the appearance rate of resistance to Isa, were assumed to be conserved when switching the dosing regimen to Q4W. Patients received Isa 10 mg/kg QW for 4 weeks then Q2W for 20 weeks, then monthly in the Isa-Pd arm. The combination dosing regimen with standard Pd was the same as in ICARIA-MM. Patients at risk at 6 months were evaluated for impact on TTP (increase >25% with absolute change of ≥5 g/L for serum M-protein compared to nadir) and PFS. The original ICARIA-MM Isa-Pd arm was also simulated with patients receiving Isa 10 mg/kg QW-Q2W to present results as median (5th-95th percentiles) difference from the original arm. Hazard ratios (HR) for the two regimens *vs* the control arm were also compared.

## 3 | RESULTS

### 3.1 | Data used for model building

Among the 307 randomized patients in the ICARIA-MM trial, 256 serum M-protein evaluable patients (128 patients/arm) were considered in this analysis. In this serum M-protein population (N = 256), median PFS was significantly longer with Isa-Pd *vs* Pd (11.4 months [95% confidence interval {CI} 8.5-13.8] vs 6.96 months [95% CI 4.4-8.5], HR 0.618, 95% CI 0.44-0.87, $P = .0048$). Similar observations on PFS and HR were obtained for the overall population (N = 307), although 16.6% of the ICARIA-MM patients could not be included in this analysis because their MM disease was characterized by urine M-protein instead of serum M-protein or on-treatment serum M-protein values were not available.

Baseline patient characteristics were balanced across arms (Table 1). Median age was 67 years (50% female). Baseline, median serum β2-microglobulin (B2MG) and serum albumin (ALB) were 3.5 mg/L and 37 g/L, respectively. High-risk cytogenetics were present in 53 (21%) patients and median estimated glomerular filtration (eGFR) rate was 70 mL/min. Most patients were IgG MM type (190 [74%]), had no plasmacytomas (232 [91%]) and 64 (25%) and 164 (64%) patients had Revised International Staging System (R-ISS) I or II stage at diagnosis, respectively. Baseline median serum M-protein was 23 g/L with a wide value range (5-95 g/L), together with various profiles during treatment. A total of 2637 serum M-protein measurements in the 256 evaluable patients were considered, with a median of 14 (range 2-22) assessments/patient. The data below LOQ accounted for 14% (22% in Isa-Pd, 6% in Pd).

**TABLE 1** Baseline demographics and patient characteristics in serum M-protein population

| | Isatuximab plus pomalidomide and dexamethasone (Isa-Pd) (n = 128) | Pomalidomide and dexamethasone (Pd) (n = 128) |
|---|---|---|
| Age, years (range) | 68 (36-83) | 66 (41-86) |
| Sex, n (%) | | |
| Female | 56 (44) | 72 (56) |
| Male | 72 (56) | 56 (44) |
| Weight (kg), median (range) | 74 (34-110) | 73 (39-140) |
| eGFR (mL/min), median (range) | 69 (30-177) | 71 (31-135) |
| R-ISS, n (%) | | |
| I | 36 (28) | 28 (22) |
| II[a] | 81 (63) | 83 (65) |
| III | 11 (9) | 17 (13) |
| Serum β2-microglobulin (mg/L), median (range) | 3.5 (1.1-27) | 3.5 (0.7-55) |
| Serum albumin (g/L), median (range) | 36.9 (16-48.7) | 37 (16.5-46.4) |
| Serum M-protein at baseline (g/L), median (range) | 22 (5-95) | 23 (5-83) |
| Type of myeloma, n (%) | | |
| IgG | 97 (76) | 93 (73) |
| Non-IgG | 31 (24) | 35 (27) |
| Plasmacytomas, n (%) | | |
| Yes | 13 (10) | 11 (9) |
| No | 115 (90) | 117 (91) |
| Cytogenetic risk at study entry, n (%) | | |
| Standard | 86 (67) | 63 (49) |
| High | 20 (16) | 33 (26) |
| Missing | 22 (17) | 32 (25) |

Abbreviations: e-GFR, estimated glomerular filtration rate; R-ISS, Revised Multiple Myeloma International Staging System (derived based on the combination of serum β2-microglobulin, albumin, cytogenetic risk and lactate dehydrogenase).
[a]As pre-specified in the study statistical analysis plan, patients with unknown cytogenetics at baseline were classified as R-ISS stage II.

### 3.2 | Modelling serum M-protein kinetics and PFS

The proposed TGI model provided an adequate fit for the longitudinal serum M-protein data of both study arms. It performed better than the Wang model.[35] In addition, the fit was improved when adding the PK of Isa compared to a K-PD model only. Twenty-six potential covariates were evaluated by testing their relationship with all the longitudinal model parameters. The final longitudinal model includes three covariates: the effects of baseline ALB and B2MG on baseline serum M-protein levels, and the non-IgG MM type on *KL*, the serum M-protein growth rate.

Regarding PFS, a log-logistic model best characterized the underlying baseline hazard distribution. Baseline covariates such as

presence of plasmacytoma, ALB and serum M-protein were significant ($P < .005$). Further information on the modelling results of longitudinal data and PFS is included in Supporting Information Tables S2 and S3.

### 3.3 | Joint modelling of serum M-protein and PFS

The joint model using the serum M-protein slope outperformed all models relying on serum M-protein in terms of BIC, with a 196-point decrease compared with the no-link model, that is, the parametric log-logistic model with no association between serum M-protein and PFS. The alternative models, based on current serum M-protein value or cumulative serum M-protein (area-under-serum M-protein), led to a BIC improvement <103. Comparison of joint models with different link functions is provided in Supporting Information Table S4. In the best, final joint model, the longitudinal model still includes the same three covariates, but only the presence of plasmacytomas remains on the PFS part. Parameter estimates obtained with the serum M-protein slope joint model are summarized in Table 2. They were reasonably well estimated with low relative standard error for both fixed effects and variance components. Although the shrinkage estimates for KDi and Ri are large (69% and 61.5%), they did not impact the covariate analysis because the sampling of conditional distribution was used instead of conditional mode estimates, allowing avoid the associated bias of large shrinkage to be avoided.[29]

The estimated link between serum M-protein slope and PFS is high at 11.9, consistent with IMWG criteria, in which the decrease in serum M-protein in response to treatment is the main component directly impacting PFS. Thus, in case of initial response, the serum M-protein decrease is associated with a current slope <0 and hence a reduced risk of progression. The relationship among serum M-protein kinetics, slope and PFS is illustrated in Figure 2 for six representative patients who either had a PFS event or not. The PFS probability decreased during tumour growth, ie, when the serum M-protein slope increased. Furthermore, the baseline covariates were found to modify parameters of serum M-protein kinetics and PFS.

**TABLE 2** Parameter estimates values (relative standard error %) of the best joint final model

| | Parameter estimates | Relative standard error (%) | Shrinkage (%) | *P* value Wald test |
|---|---|---|---|---|
| Fixed effects | | | | |
| Longitudinal submodel | | | | |
| M0 (g/L) | 17 | 3.33 | 2.9 | |
| β1 ~ ALBN | −1.41 | 15.8 | | 2.34E-10 |
| β2 ~ B2MG | 0.331 | 17 | | 3.88E-09 |
| KL ($d^{-1}$) | 0.00627 | 8.4 | 23.5 | |
| β3 ~ non_IgG | 0.55 | 27.5 | | 0.000277 |
| $KD_i$ (L $mol^{-1}$ $d^{-1}$) | 0.0138 | 8.73 | 69 | |
| $R_i$ ($day^{-1}$) | 0.00579 | 14.6 | 61.5 | |
| $KD_{pd}$ (L $mol^{-1}$ $d^{-1}$) | 0.188 | 7.36 | 24.1 | |
| $R_{pd}$ ($d^{-1}$) | 0.00952 | 10.6 | 34 | |
| Survival submodel | | | | |
| Te ($d^{-1}$) | 459 | 11.9 | | |
| S | 2.33 | 9.75 | | |
| β4 ~ PCYTOMA = Y | 0.858 | 36.3 | | 0.00591 |
| β5 ~ SlopeM | 11.9 | 7.66 | | 4.46E-39 |
| Interindividual variability standard deviation | | | | |
| ω_M0 | 50.5 | 4.73 | | |
| ω _KL | 88.7 | 6.76 | | |
| ω _$KD_i$ | 61.9 | 9.7 | | |
| ω _$R_i$ | 105 | 9.76 | | |
| ω _$KD_{pd}$ | 92 | 6.81 | | |
| ω _$R_{pd}$ | 110 | 9.33 | | |
| Residual variability | | | | |
| σ additive (g/L) | 0.411 | 7.23 | | |
| σ proportional (%) | 15 | 3.65 | | |

Abbreviations: ALBN, baseline serum albumin normalized to the upper limit value; B2MG, baseline β2-microglobulin; M0, serum M-protein at baseline, PCYTOMA, Y, presence of plasmacytomas.

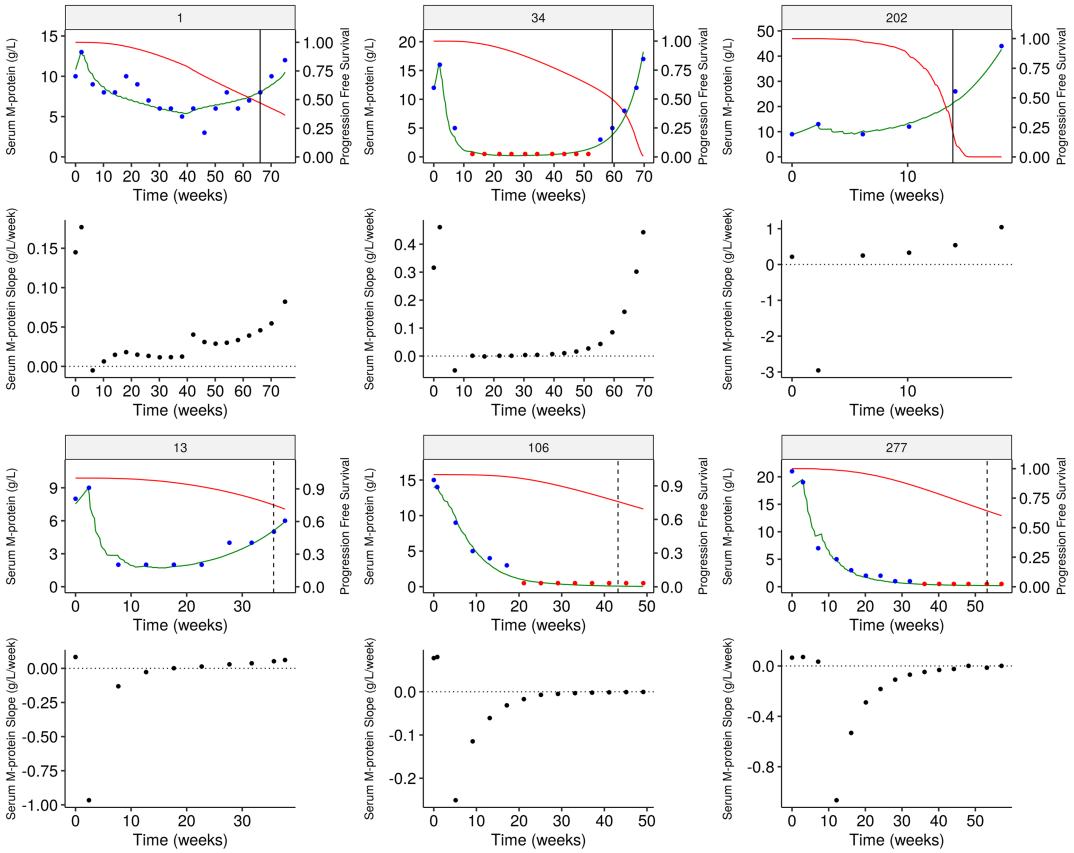


**FIGURE 2** Individual fits of serum M-protein time course and PFS probability in six illustrative patients, three with the observed event and three with the censored event. Patients in the Isa-Pd arm are in the middle and on the left; patients in the Pd arm are on the right. Blue dots denote the serum M-protein observations and red dots the BLQ observations. The green curves denote the longitudinal predictions using the joint model. The vertical lines show the status of the patients (solid, progression event occurred; dashed, censored). The red solid curves denote the PFS probability predicted by the joint model. The black curves represent the predicted value of the current slope of serum M-protein kinetics. BLQ, below the limit of quantification; Isa, isatuximab; MP, M-protein; Pd, pomalidomide and dexamethasone; PFS, progression-free survival

## 3.4 | Model evaluation

The various serum M-protein kinetic patterns could be well captured by the model and predicted PFS probability is consistent with occurrent time of progression or censored event. Figure 3 shows VPC plots generated for both longitudinal and PFS models by simulation of 1000 clinical trials under the final joint model, using the same design and patient characteristics as in the data. The model described reasonably well the observed serum M-protein and PFS data with observed median generally included in the 90% prediction interval. However, an unusual early event was observed, since the model did not capture a small group of patients who switched therapy without achieving PFS criteria. The final joint model also predicted well the HR observed between arms (Figure 4), with observed HR close to the predicted median HR. Additional goodness-of-fit plots are presented in Supporting Information Figure S1.

## 3.5 | Assessment of covariate effects

Simulations were performed to quantify the impact of each covariate using the population parameters and visualized in a typical patient (Figure 5). The effect of covariates was assessed individually by setting others to median value for continuous covariates and for the most frequent class for categorical covariates (ie, IgG type). The effect of continuous covariates, baseline ALB and B2MG, were examined for variations within the 5th-95th database percentiles.

Non-IgG MM patients had similar behaviour on serum M-protein kinetics for the first 60 weeks even with higher Isa exposure and tended to have more rapid tumour regrowth (ie, re-increase in serum M-protein) afterwards compared with IgG MM patients (Supporting Information Figure S2). Similar PFS probability is predicted for non-IgG compared to IgG MM patients. The VPC plots stratified by Ig MM type and treatment arm show agreement between model prediction and observed data (Supporting Information Figure S3).

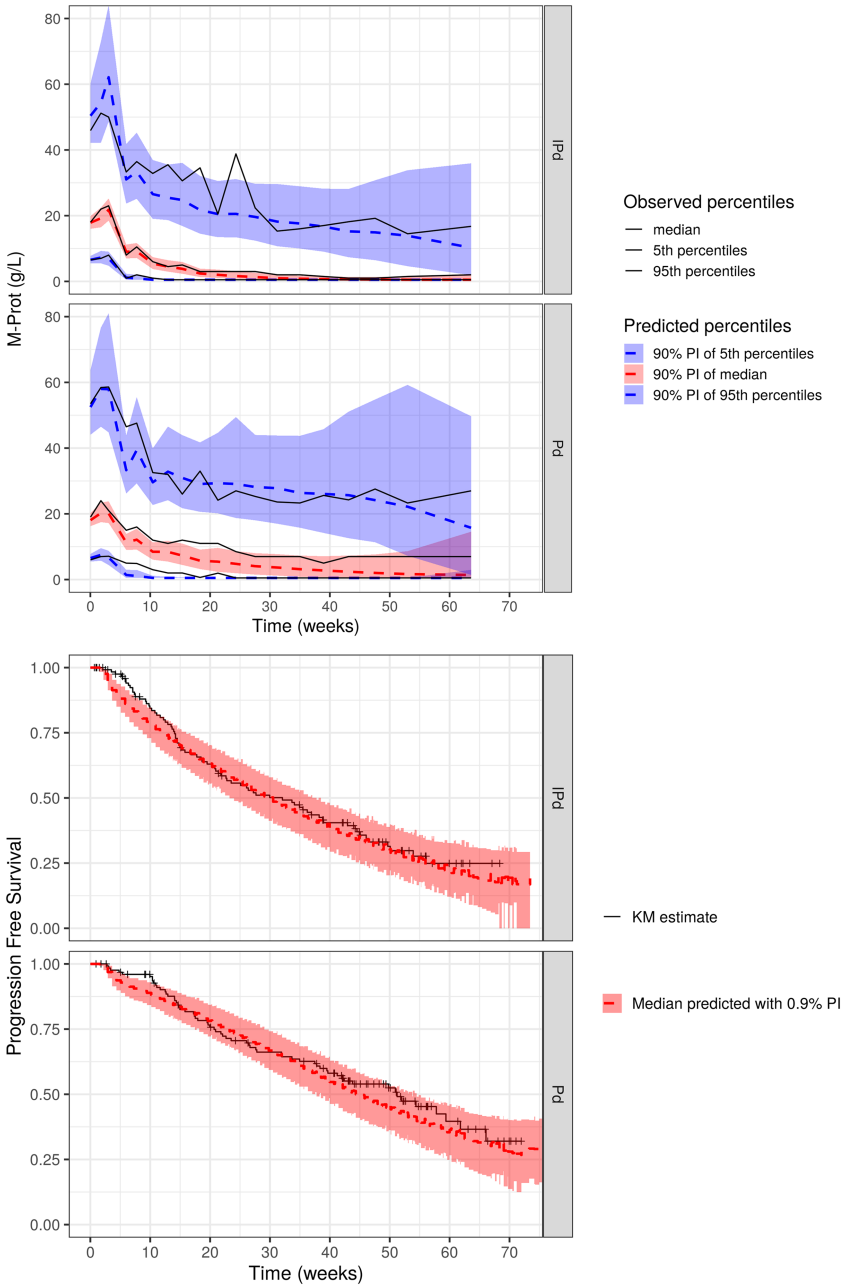


**FIGURE 3** Visual predictive checks for the longitudinal part and PFS of the final joint model. Shaded area and the dotted lines represent the 90% prediction interval and the predicted median of the 5th, 50th and 95th percentiles of simulated M-protein or PFS data (n = 1000). The solid lines represent the 5th, 50th and 95th percentiles of observed longitudinal data or the observed Kaplan-Meier estimate. CI, confidence interval; I, isatuximab; KM, Kaplan-Meier; M-P, M-protein; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; PI, prediction interval

Patients with low baseline ALB (<27 g/L) or high B2MG (>12.8 mg/L) levels are more likely to have 57% or 52% higher baseline serum M-protein, respectively, compared with patients with normal ALB or B2MG levels. The impact on the shape of M-protein profiles was a slightly faster tumour regrowth and slightly lower PFS probability at the end of treatment compared with other patients. Patients with plasmacytomas shared a similar PFS profile for 20 weeks, but tended to have lower PFS probability, up to 25% after 80 weeks.

## 3.6 | Simulation of monthly dosing regimen

In the 1000 simulated trials, the median (min-max) number of patients at risk after 6 months (ie, patients who had not progressed by 6 months) was 97 (86-107) in the Isa-Pd arm. In patients at risk at 6 months who switched to the Isa monthly dosing regimen after 6 months of QW-Q2W, median (5th-95th percentiles) progression was predicted to occur 2.29 (0.57-4.73) weeks earlier and HR predicted to be greater (0.7 vs 0.66) compared with the original Isa-Pd arm. Additionally, when considering the TTP criteria (increase in serum M-protein >25% with absolute increase >5 g/L), 44/104 (42.3%) patients who had not progressed at 6 months in the original Isa-Pd arm had their serum M-protein regrow faster and lower PFS probability with significant difference in median PFS (Wilcoxon test, *P* value = .026) (Figure 6). Evaluation of baseline patient characteristics showed that these impacted patients have more baseline disease burden, ie, higher serum M-protein, higher bone marrow plasma cells and worse prognostic characteristics, including lower eGFR, lower ALB and higher B2MG, with more frequent R-ISS II/III stage disease (80% *vs* 53.2%), compared with patients who did not progress earlier

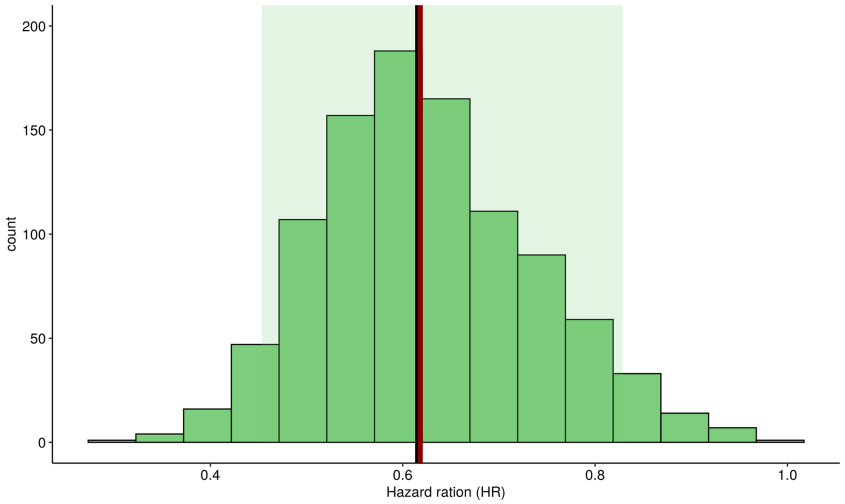


**FIGURE 4** Posterior predictive check of PFS HR using the joint model. Green zone, 95% prediction interval; black bar, predicted median HR; red bar, observed HR; PFS, progression-free survival; HR, hazard ratio

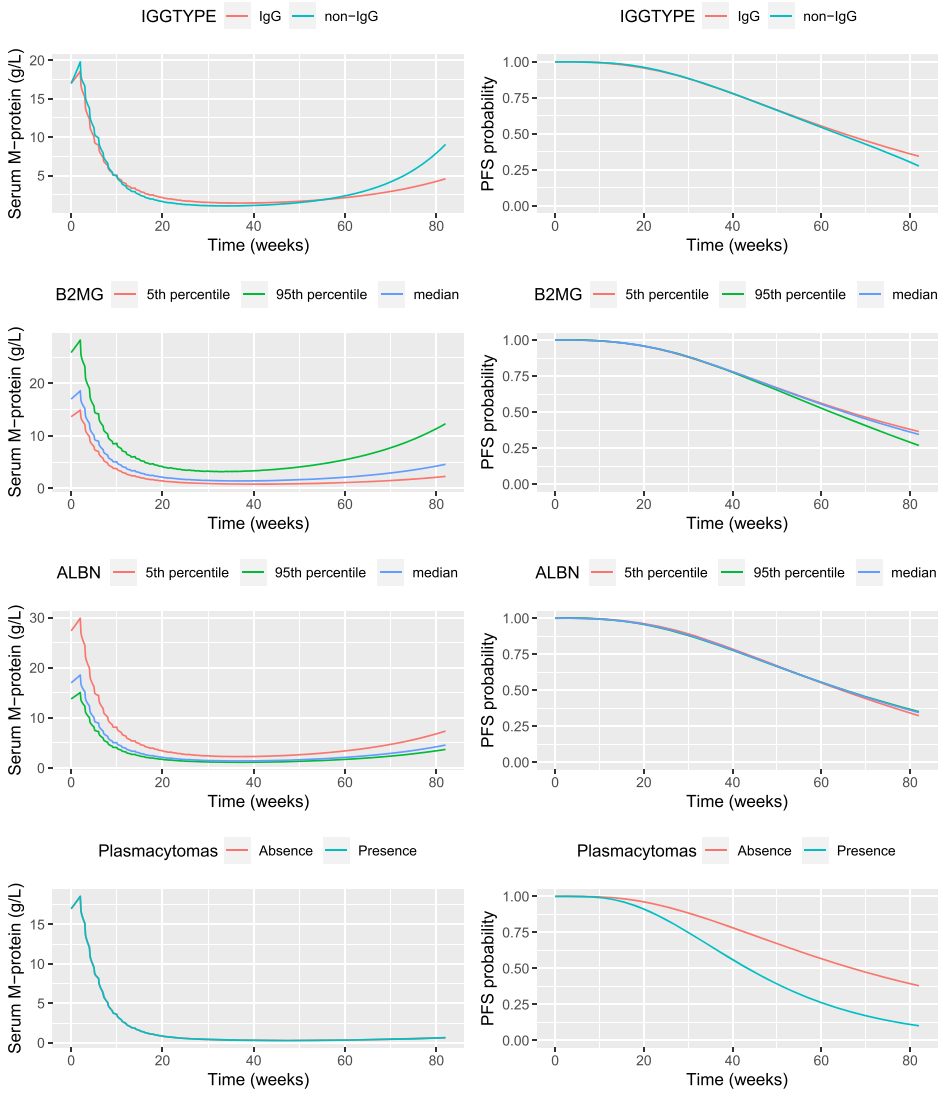


**FIGURE 5** Impact of covariate effects on serum M-protein kinetics and PFS probability of not progressed; total serum M-protein population (N = 256). ALBN, albumin; B2MG, β2-microglobulin; Ig, immunoglobulin; PFS, progression-free survival

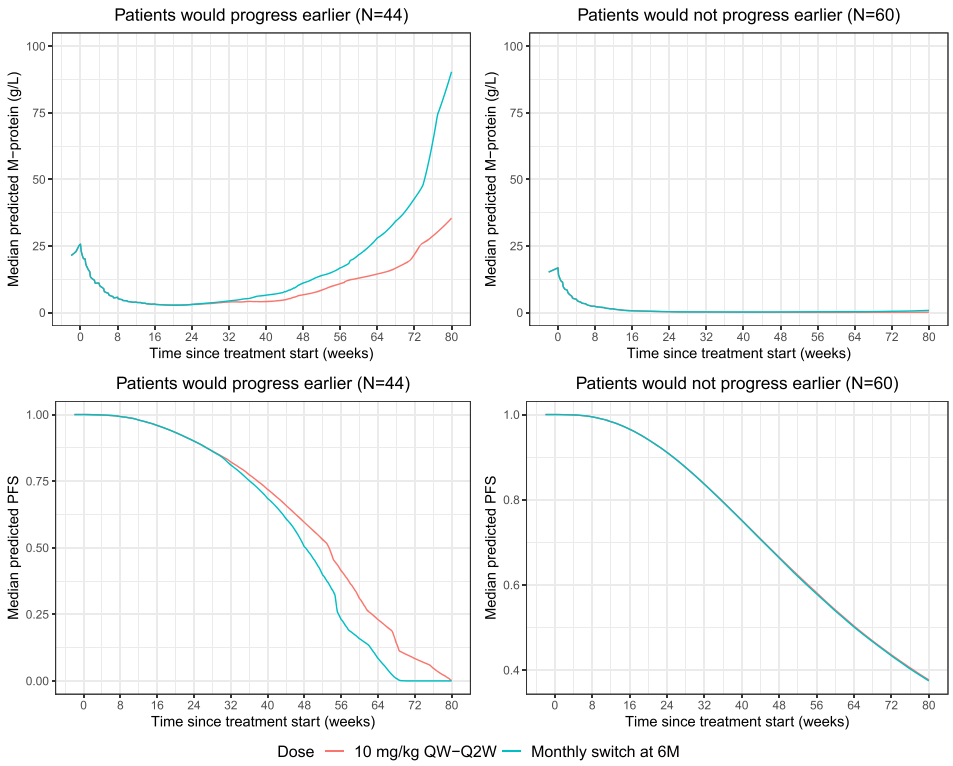


**FIGURE 6** Median predicted M-protein and PFS for patients who would progress earlier (N = 44) or would not progress earlier (N = 60). M, months; QW, weekly; Q2W every 2 weeks

(Supporting Information Figure S4). Conversely, patients with no risk of earlier progression tend to have lower tumour burden and better prognostic characteristics at baseline. Additionally, at 6 months they have significantly lower M-protein (median, 0.31 *vs* 3.04 g/L) and more patients have reached their maximum response, with a serum M-protein slope close to 0 (ie, M-protein level reached a plateau, median −0.01 *vs* −0.06 g $L^{-1}$ $d^{-1}$) and 85% of them have predicted response status of at least very good partial response.

## 4 | DISCUSSION AND CONCLUSION

A nonlinear joint model was developed in a MM setting, as joint models can provide efficient estimates and reduced bias of treatment effects on both time-to-event and longitudinal markers. We developed the TGI model using serum M-protein longitudinal data first and then the time-to-event model for PFS. Joint modelling was then performed to explore the best link between longitudinal serum M-protein and PFS. The model building was based on 256 serum M-protein evaluable patients (128 patients/arm) from the ICARIA-MM trial.

The TGI model from Claret et al was developed to describe longitudinal serum M-protein data in both arms of ICARIA-MM and compared with the Wang model, which was used for elotuzumab plus lenalidomide/dexamethasone (ELOQUENT-2) data.[25,35] We selected the Claret model, which provided a better fit and included the combined pomalidomide/dexamethasone dose and Isa PK exposure as predictors, allowing simulation of the serum M-protein response under other dosing regimens. This model accounts for three important clinical features of tumour progression in anticancer drug treatment, including the dynamics of tumour growth/production of serum M-protein, antitumour drug effect and resistance to drug effect. A more mechanism-based model incorporating distinct subpopulations of MM malignant cells would be interesting for further evaluation but requires more information on cell data.

Furthermore, we studied the impact of numerous baseline covariates on serum M-protein kinetics and risk of progression. The significant baseline covariates in the joint model were Ig MM type, ALB, B2MG and presence of plasmacytomas. Patients with low baseline ALB or high B2MG levels were more likely to have ~50% higher baseline serum M-protein and slightly faster tumour regrowth rate at the end of treatment, resulting in similar PFS profiles compared to other patients. Of note, these laboratory tests are part of the ISS/R-ISS staging systems, which are relevant for prognosis assessment, because patients with more advanced stage (ISS stage III) are less likely to respond to treatment. The presence of plasmacytomas likely induced lower PFS probability, consistent with results of exposure-response analyses.[3] Furthermore, the serum M-protein instantaneous slope was associated with PFS consistent with IMWG criteria, in which the serum M-protein decrease in response to treatment is the main component directly impacting PFS.

The Ig MM type was found to correlate with M-protein growth rate in the joint model, with faster growth rate for non-IgG patients. Simulation of typical patients indicated that non-IgG MM patients have similar behaviour on serum M-protein kinetics for the first 60 weeks, even with two-fold higher steady-state Isa exposure, but tend to have more rapid tumour regrowth afterwards and similar PFS compared to IgG MM patients. The Ig MM type was also identified as the main contributor explaining Isa PK interindividual variability, with

faster clearance in IgG MM patients resulting from competition for the neonatal Fc receptor, which protects IgG from degradation.[36–38] However, the impact of Ig MM type (IgG *vs* non-IgG) on Isa exposure does not translate into difference in treatment effect, and therefore does not appear to be clinically meaningful. This finding is consistent with the results of exposure-response and subgroup analyses which showed that there was no significant difference in treatment benefit with Isa-Pd versus Pd on PFS or ORR for IgG versus non-IgG patients.[39] Similar results were observed with daratumumab. Response rates between IgG and non-IgG MM patients were similar despite the difference in linear clearance levels between these populations (~110% higher in IgG, leading to 70% higher predicted trough serum concentrations on day 1/cycle 3 in non-IgG patients).[40]

Cytogenetics was not a significant covariate in the joint model, on either serum M-protein dynamics or PFS, in agreement with ICARIA-MM subgroup analyses, which showed that Isa-Pd provided consistent benefit versus Pd in RRMM patients, regardless of cytogenetic risk.[41]

The drug-disease modelling platform established based on ICARIA-MM data was further applied to predict the impact of using a hypothetical monthly dosing regimen after 6 months of Isa QW-Q2W in RRMM patients. In patients still on treatment, simulations of a hypothetical switch to monthly dosing after 6 months predicted progression to occur 2.3 weeks earlier compared with the original Isa-Pd arm, with 42.3% of patients having their serum M-protein regrow faster. Patients with no risk of earlier progression tended to have lower tumour burden and better prognostic characteristics at baseline, with a stable, at least very good partial response at 6 months. This modelling framework would be a useful tool to perform individual dynamic predictions in a Bayesian approach, to improve patient follow-up and early identification of most-at-risk patients, similarly to what was done for PSA kinetics and OS in prostate cancer.[42] Nevertheless, the landmark times allowing a good individual prediction will need to be further evaluated.

A major assumption in the M-protein model is that resistance develops over time and the resistance magnitude will not change when simulating alternative dosing regimens. However, resistance could be induced by drug exposure, resulting in a different resistance magnitude when switching to monthly dosing. Further investigation with more follow-up data on the relationship between drug exposure and resistance will be necessary to confirm the simulation outcome based on the current assumption.

The results of this joint modelling and simulation confirm the approved Isa QW-Q2W dosing regimen, which was selected for ICARIA-MM. Further evaluation of on-treatment switch to an Isa monthly dosing regimen should occur through a prospective clinical trial, perhaps exploring other response observations (such as minimal residual disease) as a trigger point for switching to a less frequent dosing regimen.

## ACKNOWLEDGEMENTS

The ICARIA-MM study was sponsored by Sanofi. The authors thank the participating patients and their families, and the study centres and investigators, for their contributions to the study. The authors also thank Pascale Boittet and Solenn Le-Guennec for their contributions. Medical writing support was provided by Stephanie Brillhart and Sara Mariani of Elevate Medical Affairs, contracted by Sanofi Genzyme for publication support services. This study was funded by Sanofi.

## CONTRIBUTORS

H,-T.T., G.A., B.S., H.vdV., D.S. and C.V,-F. wrote the manuscript, H,-T.T. and C.V,-F. designed the research, H,-T.T., B.S., H.vdV., D.S. and C.V,-F. performed the research, H,-T.T., N.G,-D., and C.V,-F. analysed the data. H.-T.T., N.G.-D., M.C., G.A. and J.-B.F. contributed analytical tools.

## COMPETING INTERESTS

H.-T.T., N.G.-D., M.C., J.-B.F., B.S., H.vdV., D.S. and C.V.-F. are employees of Sanofi. G.A. is an employee of Lixoft, a Simulations Plus company.

## CLINICAL TRIAL REGISTRATION

**ClinicalTrials.gov** NCT02990338.

## DATA AVAILABILITY STATEMENT

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

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**How to cite this article:** Thai H-T, Gaudel N, Cerou M, et al. Joint modelling and simulation of M-protein dynamics and progression-free survival for alternative isatuximab dosing with pomalidomide/dexamethasone. *Br J Clin Pharmacol*. 2022;88(5):2052-2064. doi:10.1111/bcp.15123