

Population Pharmacokinetic Analysis of Ixazomib, an Oral Proteasome Inhibitor, Including Data from the Phase III TOURMALINE-MM1 Study to Inform Labelling

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Abstract Ixazomib is an oral proteasome inhibitor, approved in USA, Canada, Australia and Europe in combination with lenalidomide and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy. We report a population pharmacokinetic model-based analysis for ixazomib that was pivotal in describing the clinical pharmacokinetics of ixazomib, to inform product labelling. Plasma concentration–time data were collected from 755 patients who received oral or intravenous ixazomib in once- or twice-weekly schedules in ten trials, including the global phase III TOURMALINE-MM1 study. Data were analysed using nonlinear mixed-effects modelling (NONMEM software version 7.2, ICON Development Solutions, Hanover, MD, USA). Ixazomib plasma concentrations from intravenous and oral studies were described by a three-compartment model with linear distribution and elimination kinetics, including first-order linear absorption with a lag time describing the oral dose data. Body surface area on the volume of the second peripheral compartment was the only covariate included in the final model. None of the additional covariates tested including body surface area (1.2–2.7 m²), sex, age (23–91 years), race, mild/moderate renal impairment and mild hepatic impairment

were found to impact systemic clearance, suggesting that no dose adjustment is required based on these covariates. The geometric mean terminal disposition phase half-life was 9.5 days, steady-state volume of distribution was 543 L and systemic clearance was 1.86 L/h. The absolute bioavailability of an oral dose was estimated to be 58%.

Key Points

Ixazomib pharmacokinetic data from 755 adult patients enrolled across ten studies were adequately described by a three-compartment model with linear distribution and elimination kinetics, including first-order linear absorption with a lag time describing the oral dose pharmacokinetic profile.

The geometric mean terminal disposition phase half-life was 9.5 days, steady-state volume of distribution was 543 L and systemic clearance was 1.86 L/h. The absolute bioavailability of an oral dose was estimated to be 58%.

No ixazomib dose adjustment is required based on body surface area (1.2–2.7 m²), sex, age (23–91 years), race, mild or moderate renal impairment, mild hepatic impairment, and smoking status.

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1 Introduction

Ixazomib is the first oral proteasome inhibitor to enter clinical investigation in hematologic and non-hematologic malignancies [1]. It is approved in the USA, Canada,

Australia and Europe in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy, based on results from the global phase III, randomised, double-blind, placebo-controlled trial, TOURMALINE-MM1 [2–6]. In the TOURMALINE-MM1 study, ixazomib plus lenalidomide-dexamethasone treatment was associated with a 35% improvement in progression-free survival vs. placebo plus lenalidomide-dexamethasone [5]. Ixazomib is also undergoing phase III investigation in patients with newly diagnosed MM in combination with lenalidomide and dexamethasone (NCT01850524); as single-agent maintenance therapy in MM (NCT02181413 and NCT02312258); and in patients with relapsed/refractory primary systemic amyloidosis in combination with dexamethasone (NCT01659658).

Clinical studies have demonstrated that ixazomib is rapidly absorbed, with a median time to maximum plasma concentration of 1 h post-dose, and exhibits dose-proportional increases in exposure (area under the concentration–time curve [AUC]) [7, 8]. After once-weekly repeat-dose administration, the accumulation ratio for AUC was demonstrated to be approximately 2 [8]. Metabolism by both cytochrome p450 (CYP) enzymes and non-CYP proteins is expected to be the major clearance (CL) mechanism for ixazomib. At clinically relevant ixazomib concentrations, *in vitro* studies using human cDNA-expressed CYP isozymes showed that no specific CYP isozyme predominantly contributed to ixazomib metabolism [2]. Following administration of a single oral dose of radio-labelled ixazomib to five patients with advanced cancer, 62% of the administered radioactivity was excreted in urine and 22% in feces [2, 9]. In a study examining ixazomib administration after a high-calorie high-fat meal, the rate and extent of ixazomib absorption was decreased, with a 28% reduction in total systemic exposure (AUC) and a 69% reduction in peak plasma concentration, thereby supporting administration at least 1 h before or at least 2 h after food [10]. Additionally, a reduced dose of ixazomib (3 mg) in patients with severe renal impairment and in patients with moderate or severe hepatic impairment is supported by the results of two phase I studies in these special patient populations [11, 12].

Ixazomib has been investigated after both intravenous (IV) and oral administration, and using both once- and twice-weekly dosing schedules, for patients with hematologic and non-hematologic malignancies. In early phase I studies, ixazomib was administered using body surface area (BSA)-based dosing. A population pharmacokinetic (PK) analysis of ixazomib was conducted early in clinical development, based on data from four phase I clinical trials available at the time [13]. This analysis supported the switch from BSA-based dosing to fixed dosing. Since this

initial analysis, substantially more PK data have become available from multiple ixazomib clinical trials conducted across global patient populations, including the TOURMALINE-MM1 study [5]. Accordingly, a more robust analysis of all available PK data was performed to identify any patient characteristics that may contribute to variability in the pharmacokinetics of ixazomib. Results from this analysis were pivotal in describing the clinical pharmacokinetics of ixazomib in the US prescribing information and the European Summary of Product Characteristics [2, 6]. Furthermore, these results can be used to guide future drug development and dosing decisions in the ongoing and future clinical investigations of ixazomib across patient populations and indications.

The objectives of this analysis were to develop a population PK model based on available data from relevant phase I, I/II, and III ixazomib studies, including identification and quantification of statistically significant and clinically relevant covariates on population PK parameters, and to estimate individual PK parameters for patients included in the analysis based on the final population PK model.

2 Methods

2.1 Data Collection

Ixazomib plasma concentration–time data were collected from adult patients with advanced hematologic or non-hematologic malignancies (i.e., MM, lymphoma, light-chain amyloidosis or various solid tumours) who had participated in one of ten clinical trials (Table 1; [5, 7, 8, 13–19]). Full eligibility criteria for study participants are described in each of the original publications. Patients received oral (BSA-based or fixed) or IV (BSA-based) doses of ixazomib. Ixazomib was administered using once-weekly (days 1, 8, and 15 of a 28-day cycle) or twice-weekly (days 1, 4, 8, and 11 of a 21-day cycle) dosing regimens. All procedures performed in studies involving human participants were in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and appropriate regulatory requirements.

Plasma concentrations of ixazomib were measured pre-dose and at various timepoints post-dose during ixazomib treatment (Supplementary Table 1). Concentrations of ixazomib were measured using a validated liquid chromatography/tandem mass spectrometry assay. A reverse-phase gradient method, running at a flow rate of 0.3 mL/min on a Fortis Phenyl, 2.1 × 50 mm, 5- μ m column (Fortis Technologies Ltd, Neston, UK), provided sample stacking and separation for the analytes. Ixazomib and the internal standard ($^{13}\text{C}_9$ -ixazomib) were ionised in the positive ion spray mode and detected through multiple

Table 1 Studies included in the population PK analysis

Study (phase)	Clinical Trials.gov identifier	Patient population	<i>n</i> ^a	Regimen	Ixazomib dose ^b (mg)
C16001 (I) ^c	NCT00830869	Advanced non-hematologic malignancies	80	TW, IV, single agent	Dose escalation (0.2–4.8) ^d
C16002 (I) ^c	NCT00893464	Lymphoma	28	W, IV, single agent	Dose escalation (0.23–6.8) ^d
C16003 (I) ^c	NCT00932698	Relapsed and/or refractory MM	52	TW, PO, single agent	Dose escalation (0.4–4.8) ^d
C16004 (I) ^c	NCT00963820	Relapsed and/or refractory MM	51	W, PO, single agent	Dose escalation (0.2–8.9) ^d
C16005 (I/II)	NCT01217957	Newly diagnosed MM	62	W, PO, combination with len/dex	Phase I: dose escalation (2.9–10.6) ^d Phase II: 4.0
C16007 (I)	NCT01318902	Relapsed or refractory light-chain amyloidosis	15	W, PO, single agent	Dose escalation (4.0–5.5)
C16008 (I/II)	NCT01383928	Newly diagnosed MM	63	TW, PO, combination with len/dex	Phase I: dose escalation (3.0–3.7) Phase II: 3.0
C16010/ TOURMALINE MM-1 (III)	NCT01564537	Relapsed and/or refractory MM	347	W, PO, combination with len/dex	4.0
C16013 (I)	NCT01645930	East Asian patients with relapsed and/or refractory MM	43	W, PO, combination with len/dex	4.0
TB-MC010034 (I)	NA	Japanese patients with relapsed and/or refractory MM	14	W, PO, single agent or combination with len/dex	4.0

BSA body surface area, *Dex* dexamethasone, *IV* intravenous, *Len* lenalidomide, *MM* multiple myeloma, *NA* not applicable, *PK* pharmacokinetic, *PO* oral, *TW* twice-weekly: 21-day cycle with doses on days 1, 4, 8, 11; *W* weekly: 28-day cycle with doses on days 1, 8, 15

^a Patients included in the population PK analysis

^b Numbers in brackets show the range of starting doses administered to patients

^c Studies included in the initial population PK analysis [13]

^d BSA-based dosing

reaction monitoring of mass transition pairs at 343.1 → 109.0 *m/z* and 352.1 → 115.0 *m/z*, respectively. Assay linearity was achieved over a concentration range of 0.5–500 ng/mL for ixazomib, and precision ranged from 1.7 to 6.1% coefficient of variation, with a bias of –4.0 to 2.3% [12].

Patients with at least three PK samples with concentrations above the lower limit of quantification (LLOQ) were included in the analysis. Ixazomib concentrations below the limit of quantification during active treatment were imputed as LLOQ/2 (0.25 ng/mL) or discarded according to the modified M6 method, in which only the first sample of a sequence of samples below the limit of quantification was set to LLOQ/2 and subsequent samples in the sequence below the limit of quantification were discarded [20].

2.2 Population Pharmacokinetic Modeling

Population PK data analysis was performed using NONMEM software (Version 7.2, ICON Development Solutions, Hanover, MD, USA [21]) for non-linear mixed-effects models, running under Perl-speaks-NONMEM (PsN [22] 4.2.0) on a grid of CentOS 7.0 linux

servers, and the Intel Fortran compiler, Version 12. Analysis of results was performed using R (Version 3.0.0 or later [23]). The NONMEM models were developed to describe the log-transformed ixazomib concentrations, and estimates were based on the first-order conditional estimation method. The model was developed in a step-wise manner, guided by a pre-specified analysis plan. First, the structural model was optimised by fitting a fixed-effects model to the observed data. Subsequently, the statistical model describing the within- and between-patient variability was developed, resulting in the base model. Finally, statistically significant and clinically relevant covariates were added to the base model to produce the final model. The population PK model was developed using both IV and oral data. Structural model selection proceeded from a one-compartment model to two- and three-compartment models, and was also guided by the results of the first population PK analysis that clearly demonstrated multi-phasic disposition kinetics of ixazomib, which were best described by a three-compartment model [13].

Inter-individual variability was implemented by exponential random-effect models, corresponding to log-normally distributed individual parameters:

$$\theta_i = \theta_{TV,i} * \exp(\eta_i), \quad (1)$$

where θ_i and $\theta_{TV,i}$ are the individual and typical values of the parameter, η_i is an individual-level random variable sampled from a normal distribution with a mean of zero and variance of ω^2 , and represents the i th individual's deviation from the typical value.

The residual variability was described by an additive error model on the log-transformed concentrations:

$$\log(Y_{ik}) = \log(C_{ik}) + \varepsilon_{ik}, \quad (2)$$

where Y_{ik} is the k th observed ixazomib concentration in the i th individual, C_{ik} is the corresponding individual model-predicted concentration, and ε_{ik} is the residual error component sampled from $N(0, \sigma^2)$. The variance of the residual error was either constant or time dependent [24] with variance defined as a parametric function of time:

$$\text{sd}(\varepsilon) = \text{SD}_0 + (\text{SD}_1 - \text{SD}_0) * \exp(-K_{SD} * \text{time} [h]), \quad (3)$$

where $\text{sd}(\varepsilon)$ is the standard deviation of the unexplained random variability, parameterized as a function of the standard deviation at the beginning of the treatment period (SD_1), the asymptotic standard deviation (SD_0) and the rate constant of change in SD (K_{SD}).

Based on typical and individual parameter estimates, the characteristic half-lives associated with a three-compartment model ($t_{1/2,\alpha}$, $t_{1/2,\beta}$ and $t_{1/2,\gamma}$), as well as the steady-state volume of distribution were derived [25].

2.3 Covariate Analysis

Covariates were tested for statistical significance and clinical relevance, based on the pre-defined list of relevant parameter-covariate relationships (Supplementary Table 2). All covariates were baseline covariates, except concomitant administration of CYP-modulatory drugs, which was included as a time-dependent covariate. Covariates were tested on CL and volume parameters that included a random effect. Model selection was done on the basis of a log-likelihood ratio test by iteratively adding the most significant of the evaluated covariate-parameter relationships until no more statistically significant covariates (at $p = 0.01$) that also led to a reduction of at least 10% in the corresponding random-effect variance were found. Subsequently, the least significant covariate was eliminated in a backward deletion procedure until no more non-significant covariates (at $p = 0.001$) were left in the model.

Continuous covariates were included in the population PK model as power functions, while categorical covariates were implemented as factors:

$$\theta_{TV,i} = \theta_{TV,POP} * (X_{Cont,i} / \text{median}[X_{Cont,i}])^{\theta_1} * (1 + X_{Cat,i} * \theta_2), \quad (4)$$

Table 2 Summary of covariate values for patients in the population PK analysis dataset

Covariate	Median (range) or categories (%)
Continuous	
Age (years)	65 (23–91)
Serum albumin (g/L)	39 (12–55)
Aspartate aminotransferase (U/L)	22 (4–127)
Total bilirubin (μM)	7 (1.71–39.3) ^a
BSA (m^2)	1.88 (1.23–2.67)
Creatinine clearance ^b (mL/min)	86.8 (25.8–297)
Hematocrit (proportion of 1)	0.35 (0.15–0.54)
Hemoglobin (g/dL)	11.6 (4.6–16.8)
Body weight (kg)	75.5 (36.7–151)
Categorical	
<i>Len/dex combination</i>	
Single agent	29.9
Len/dex combination	70.1
<i>Race</i>	
White	79.9
Black	5.56
Asian	11.7
Other	2.91
<i>Sex</i>	
Female	42.4
Male	57.6
<i>Smoking status</i>	
Never	33.1
Current	4.37
Former	18.5
Unknown	44.1

BSA body surface area, *Len/dex* lenalidomide-dexamethasone, PK pharmacokinetic

^a 0.4 (0.1–2.3) mg/dL

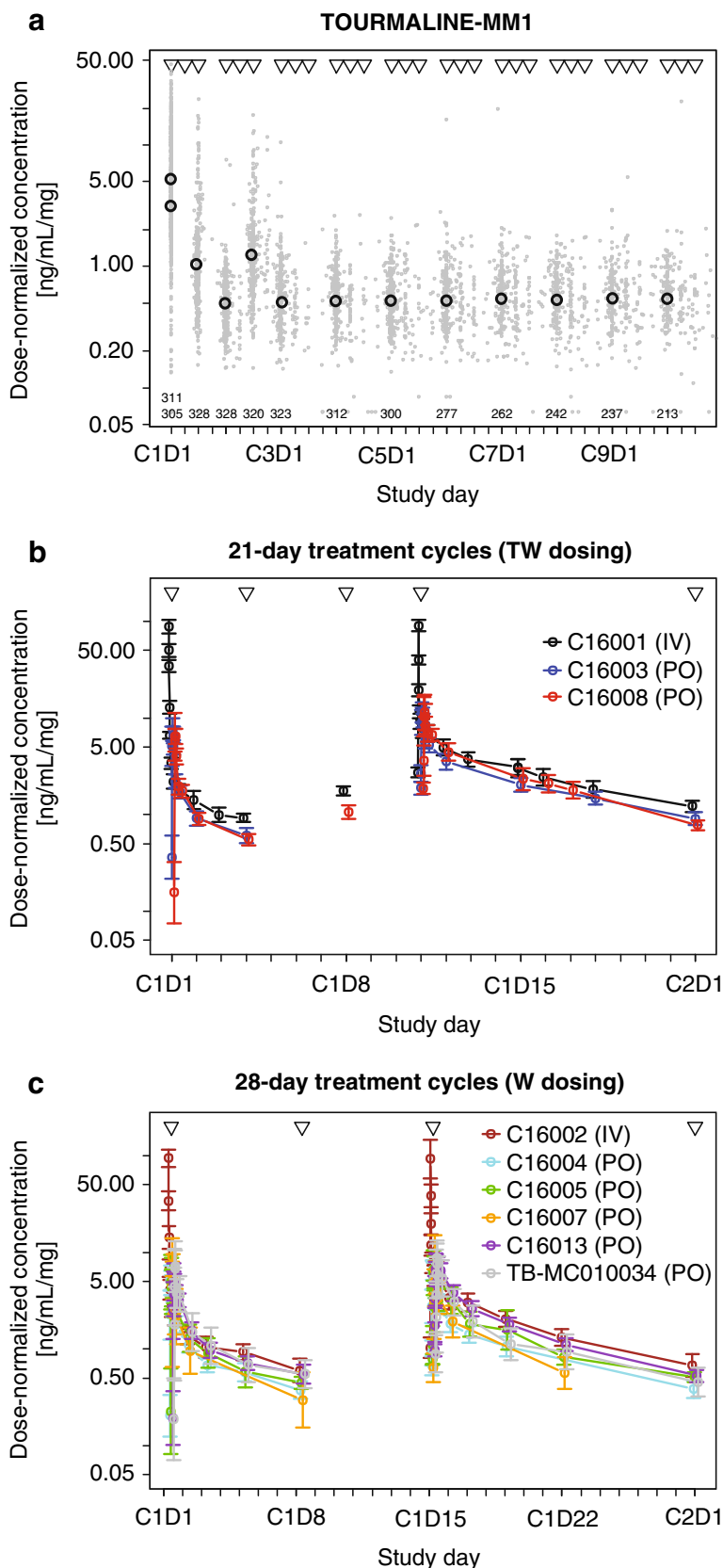
^b Creatinine clearance estimated using the Cockcroft–Gault equation [33]

where $\theta_{TV,i}$ is the typical parameter for patient i , defined as a function of the population typical value, $\theta_{TV,POP}$ and the individual contributions from continuous (X_{Cont}) and binary (X_{Cat} , with values 0 and 1) covariates. θ_1 and θ_2 represent the respective covariate coefficients.

2.4 Model Evaluation

The objective function value (OFV) was used to initially evaluate whether alternative models represented an improvement in overall fit compared with the candidate model. If the alternative model better fit the data, more elaborate diagnostic tools were used to further assess the

Fig. 1 Geometric mean of dose-normalised ixazomib concentrations observed in: **a** TOURMALINE-MM1 binned by visit number (*open black circles*) with individual observations (*grey dots*) at the actual sampling times. *Triangles* indicate protocol-specified dose times and numbers indicate the number of PK samples included in each geometric mean calculation. **b** Cycle 1 in studies with 21-day treatment cycles (TW dosing) binned by protocol-specified sampling time. *Triangles* indicate protocol-specified dose times. *Error bars* show 95% CI of the geometric mean. **c** Cycle 1 in studies with 28-day treatment cycles (W dosing), binned by protocol-specified sampling time. *Triangles* indicate protocol-specified dose times. *Error bars* show 95% CI of the geometric mean. *CI* confidence interval, *IV* intravenous, *PK* pharmacokinetic, *PO* oral, *TW* twice weekly, *W* weekly



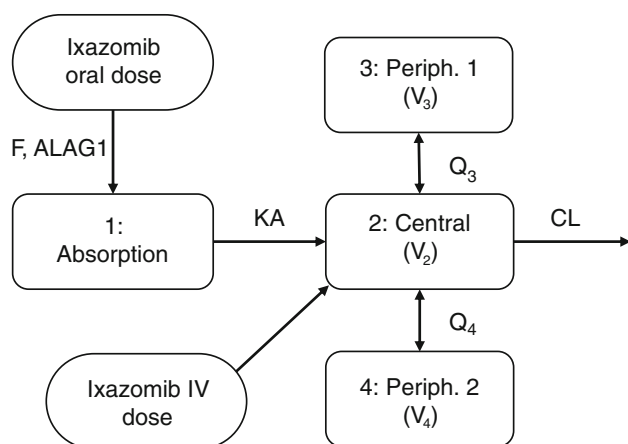


Fig. 2 Structural model describing the pharmacokinetics of ixazomib. *ALAG1* absorption lag time, *CL* clearance, *F* absolute bioavailability of an oral ixazomib dose, *IV* intravenous, *KA* absorption rate constant, Q_3 first inter-compartmental clearance, Q_4 second inter-compartmental clearance, V_2 central volume of distribution; V_3 volume of distribution of first peripheral compartment, V_4 volume of distribution of second peripheral compartment

quality of the model. Alternative models were compared based on the overall model fit (i.e., NONMEM OFV), precision of parameter estimates (% relative standard error), condition number, random-effect and residual error model variances, and based on the following diagnostic tools: goodness-of-fit plots, prediction-corrected visual predictive check (VPC) and bootstrap. In the VPC, quartiles of prediction-corrected observed data were superimposed on the 1000 corresponding simulated datasets to demonstrate the ability of the model to adequately describe the mean trend and variability in the observed data. Model robustness and parameter estimates were assessed by bootstrap based on 1000 resampled datasets (with replacement).

3 Results

3.1 Data Summary

Pharmacokinetic data were available from 755 adult patients, including 632 patients with MM, 80 patients with advanced solid tumours, 28 patients with lymphoma and 15 patients with light-chain amyloidosis (Table 1; [5, 7, 8, 13–19]); 347 patients were treated in the phase III TOURMALINE-MM1 study, in which patients with relapsed/refractory MM received once-weekly oral ixazomib in combination with lenalidomide and dexamethasone. Patients in studies C16005, C16008, C16013 and a cohort in TB-MC010034 also received ixazomib in combination with lenalidomide and dexamethasone ($n = 168$); all other studies used single-agent ixazomib ($n = 240$).

Most patients received oral ixazomib ($n = 647$), but patients in two phase I studies received IV ixazomib ($n = 108$); 560 patients received weekly dosing and 195 patients received twice-weekly dosing.

A total of 10,199 PK samples were available; 172 (1.7%) were flagged for exclusion from the analysis because of suspected date and/or sampling time recording errors. Of the 354 (3.5%) samples below the limit of quantification, 124 (1.2%) samples were flagged for exclusion, while the remaining 230 samples (2.3%) were simply imputed to LLOQ/2. Given the small number of samples below the limit of quantification, a more complex imputation method (e.g., M3, M4) was not examined as this would have increased the complexity of the model without providing substantial improvements in the model fit. The demographics and baseline characteristics of patients included in the analysis dataset are summarised in Table 2.

Geometric mean and individual dose-normalised PK data obtained from the phase III TOURMALINE-MM1 study are shown in Fig. 1a. Dose-normalised ixazomib concentration–time profiles for phase I and I/II studies with 21-day treatment cycles (twice-weekly ixazomib dosing) and 28-day treatment cycles (weekly ixazomib dosing) are shown in Fig. 1b and c, respectively. In all three plots, the observed ixazomib concentration was normalised by dividing each individual sample concentration by the preceding ixazomib dose. Plots of raw concentrations (not dose normalised) are shown in Supplementary Figure 1.

3.2 Population Pharmacokinetic Model Development

The observed ixazomib plasma concentration–time data after IV or oral administration were adequately described by a three-compartment model with linear distribution and elimination kinetics, including first-order linear absorption with a lag time describing the oral dose PK profile (Fig. 2). The developed model included log-normally distributed patient-level random effects on systemic CL, absolute bioavailability of an oral dose (F) and the volume of the second peripheral compartment (V_4). Individual CL and F were correlated, with coefficient of correlation estimated at 82%. The value of F estimated for patients receiving IV ixazomib was based on the estimated correlation between F and CL. Residual unexplained variability of the log-transformed concentrations was described by an additive error model with time-varying variance described by an exponential decline in the standard deviation (SD) from a starting level (SD_1) towards a steady-state plateau (SD_0). This residual error model has been previously described by Karlsson et al. [24] and was implemented in the analysis, as a constant additive residual error model showed bias in the

conditional weighted residuals and VPCs with respect to time. The SD in the time-varying error model decreases over the first 2–4 h post-dose towards a plateau, reflecting the lower variability in the observed data at later time points.

A covariate model was built based on pre-specified covariate-parameter relationships (Supplementary Table 2). Covariates were only tested on CL and volume parameters that included a random effect. The improvement in OFV, statistical significance, and change in the corresponding inter-individual variances associated with the CL and V_4 parameters following univariate covariate additions are shown in Supplementary Table 3. The addition of univariate covariates corresponded to the first step in the forward addition procedure. Among the parameter-covariate relationships tested, only BSA and body weight met the predefined selection criteria on V_4 by leading to a

statistically significant improvement of the model fit, and reducing the random-effect variance by at least 10%. In fact, no other covariates reduced the random-effect variance meaningfully, even when a more conservative criterion of relative reduction of inter-individual variability by $\geq 5\%$ was used. Because BSA and body weight are strongly correlated body size-related covariates, only one was included in the model. BSA had a small advantage to body weight, both in terms of reducing the OFV and the random-effect variance. Consequently, BSA was included on V_4 as the only covariate in the final model.

The PK parameter values estimated for the final population PK model are presented in Table 3. The final model provided parameter estimates with good precision (relative standard error $\leq 22\%$). Furthermore, shrinkage of individual random effects was reasonable ($\leq 37\%$) with shrinkage of individual CL estimates of 21% in the final model. The

Table 3 Model parameters estimated for the final model

Fixed-effect parameters	Estimate	RSE (%)	Untransformed parameter
Absorption rate constant (log K_a)	-1.09	8	0.34/h $\sim t_{1/2} = 124$ min
Systemic clearance (log CL)	0.62	7	1.86 L/h
Central volume of distribution (log V_2)	2.62	4	13.7 L
Absolute bioavailability (log F)	-0.55	9	58%
First inter-compartmental clearance (log Q_3)	1.65	7	5.18 L/h
Volume of the first peripheral compartment (log V_3)	5.73	1	309 L
Second inter-compartmental clearance (log Q_4)	3.26	2	26.1 L/h
Volume of the second peripheral compartment (log V_4)	5.32	1	205 L
Absorption lag time (log T_{LAG})	-1.52	0	13 min
Impact of BSA on V_4 ($V_4[BSA]$)	2.06	18	-37 and +46% at the 5th and 95th percentile (1.5 and 2.25 m ²) on V_4 relative to median BSA (1.87 m ²)
Random-effect parameters	Estimate	RSE* (%)	η shrinkage (%)
Inter-individual variability on log CL	44%	11	21
Inter-individual variability on log F	73%	8	13
Correlation between log CL and log F	82%	11	
Inter-individual variability on log V_4	79%	12	37
Initial sd of the residual error (SD_1)	1.90	11	
Steady state sd of the residual error (SD_0)	0.46	3	
Time constant of residual error sd (K_{SD})	0.84	22	$t_{1/2} = 50$ min
Residual random variability			7

Inter-individual variability shown as % coefficient of variation. *rse inter-individual variability is derived as $100\% \cdot se_{\omega_2} / \omega^2$

Model parameters and RSEs correspond to the raw estimates provided by NONMEM. The untransformed parameters show the corresponding pharmacokinetic parameters

BSA body surface area, CL systemic clearance, F bioavailability, K_{SD} rate constant of change in SD, Q_3 first inter-compartmental clearance, Q_4 second inter-compartmental clearance, RSE relative standard error, sd standard deviation, SD_0 asymptotic standard deviation, SD_1 standard deviation at the beginning of the treatment period, T_{LAG} absorption lag time, V_2 central volume of distribution, V_3 volume of distribution of first peripheral compartment, V_4 volume of distribution of second peripheral compartment

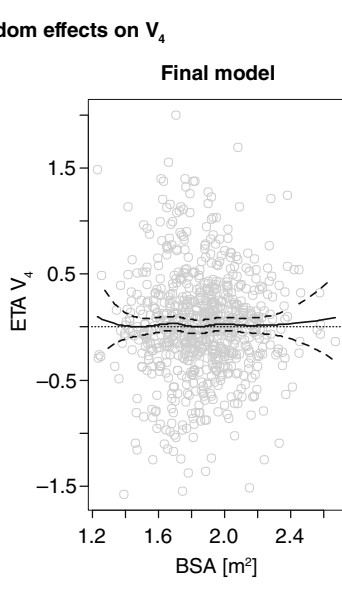
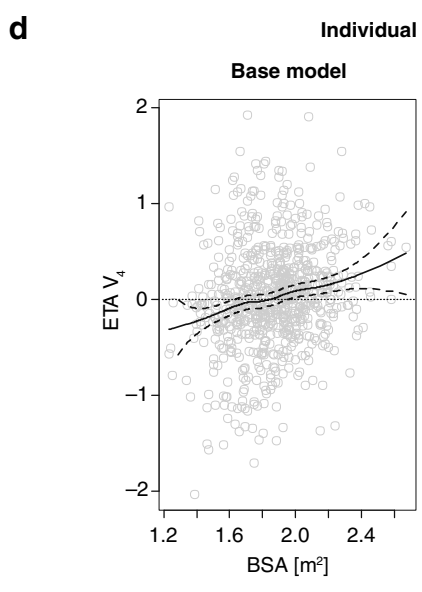
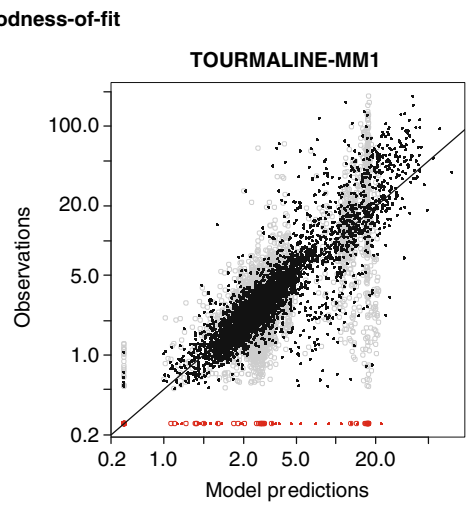
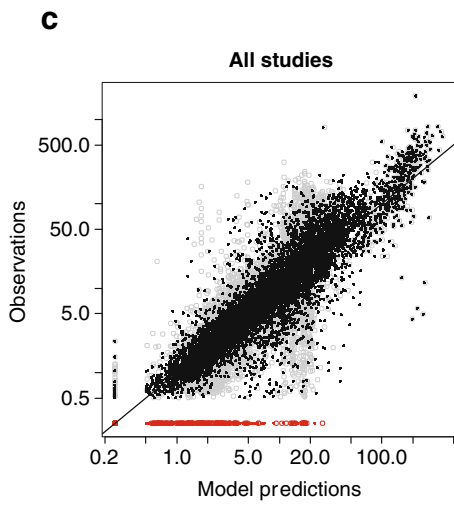
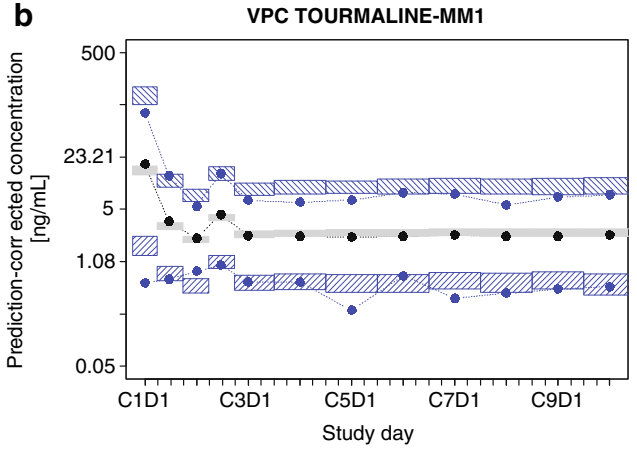
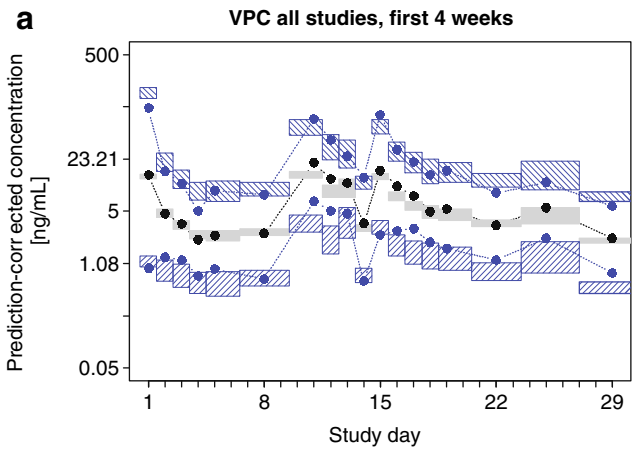


Fig. 3 Diagnostic plots: **a** VPC showing data from the first 4 weeks of all studies based on 1000 simulated datasets. Median and 2.5th–97.5th percentile interval of prediction-corrected observed ixazomib concentrations (*black and blue dots*, respectively) model simulations (95% CI, *grey and blue hatched areas*). **b** VPC showing data from TOURMALINE-MM1 based on 1000 simulated datasets. Median and 2.5th–97.5th percentile interval of prediction-corrected observed ixazomib concentrations (*black and blue dots*, respectively) model simulations (95% CI, *grey and blue hatched areas*). **c** Goodness-of-fit of the final model based on data from all studies (*left*) and data from TOURMALINE-MM1 (*right*). *Black and grey dots* show observed data vs. individual and population predictions, respectively. *Red dots* indicate observed data below the limit of quantification and the *solid line* is the line of unity. **d** Individual random effects on V_4 based on the base model (*left*) and final model (*right*) shown vs. body surface area. *Solid and dashed lines* show a LOESS smooth curve with corresponding 95% CI. *BSA* body surface area, *CI* confidence interval, V_4 volume of distribution of second peripheral compartment, *VPC* visual predictive check

geometric mean (95% confidence interval) of the individual estimated terminal disposition phase half-life ($t_{1/2,\gamma}$) was 9.53 (9.32–9.75) days and the steady-state volume of distribution was 543 (534–551) L. These estimates were similar to the population estimates for $t_{1/2,\gamma}$ (9.35 days) and steady-state volume of distribution (527 L). The absolute oral bioavailability (F) was estimated to be 58%.

3.3 Pharmacokinetic Model Assessment

To evaluate the appropriateness of the statistical components of the final model, a prediction-corrected VPC was performed [26]. Figure 3 shows a VPC based on data from the first 4 weeks of all studies (Fig. 3a) and from the phase III TOURMALINE-MM1 study (Fig. 3b). Apart from a few time bins, the observed median and 2.5th–97.5th percentiles of data fall within the corresponding 95% confidence interval of the model simulations, indicating that the model adequately describes the central tendency and total variability of the data.

Figure 3c shows the goodness-of-fit plots of the final model based on data from all studies and data from the phase III TOURMALINE-MM1 study. The plots show that both population and individual predictions vs. the observed data scatter randomly around the line of unity, indicating an unbiased fit. As expected, individual predictions are noticeably closer to the line of unity than corresponding population predictions, illustrating the impact of the random-effects model for explaining variability in the observed data. Figure 3d shows the patient-specific random effects (ETA) on V_4 estimated with the base and final models, plotted against individual BSA, and confirms that including BSA as a covariate on V_4 in the final model removes the trend in the random effect on V_4 vs. BSA that was observed with the base model.

Based on the developed final model, the individual predicted exposure following a single oral 4-mg ixazomib dose

was calculated using the individual estimated CL and absolute bioavailability as $AUC_{\infty} = 4 \text{ mg} \times F_y/CL_i$. To evaluate trends in individual predicted exposure, $AUC_{\infty,i}$ was described using linear regression models including individual covariates as predictors. This corresponds to a graphical covariate screening where individual parameters are plotted vs. covariate values. If no trend is observed, the parameter can be described by the population typical value and random variability. Figure 4 shows the correlation between key continuous covariates and individual predicted exposure and the prediction of the linear regression at the 5th and 95th percentile of continuous covariates relative to the median value. Across the analysis population, the 5th and 95th percentiles of individual predicted exposures were –50 and +98% relative to the median AUC_{∞} . For each continuous covariate, the magnitudes of percent difference in AUC_{∞} at the 5th or 95th percentiles relative to the AUC_{∞} at the median of individual covariate values were <20%, and are therefore well below the variability in AUC_{∞} in the study population. This was consistent with these covariates not being identified as statistically or clinically meaningful covariates on CL. Similarly, as shown in Fig. 5, for categorical covariates, the magnitude of AUC_{∞} in different categories relative to the most common category were <20% in all cases with the exception of Asian race, where the mean AUC_{∞} was 35% higher than in White race group. However, there was substantial overlap in exposure between the White and Asian race groups. Taken together, these analyses confirm the absence of clinically meaningful effects of the evaluated covariates on the systemic exposure (AUC_{∞}) of ixazomib in cancer patients.

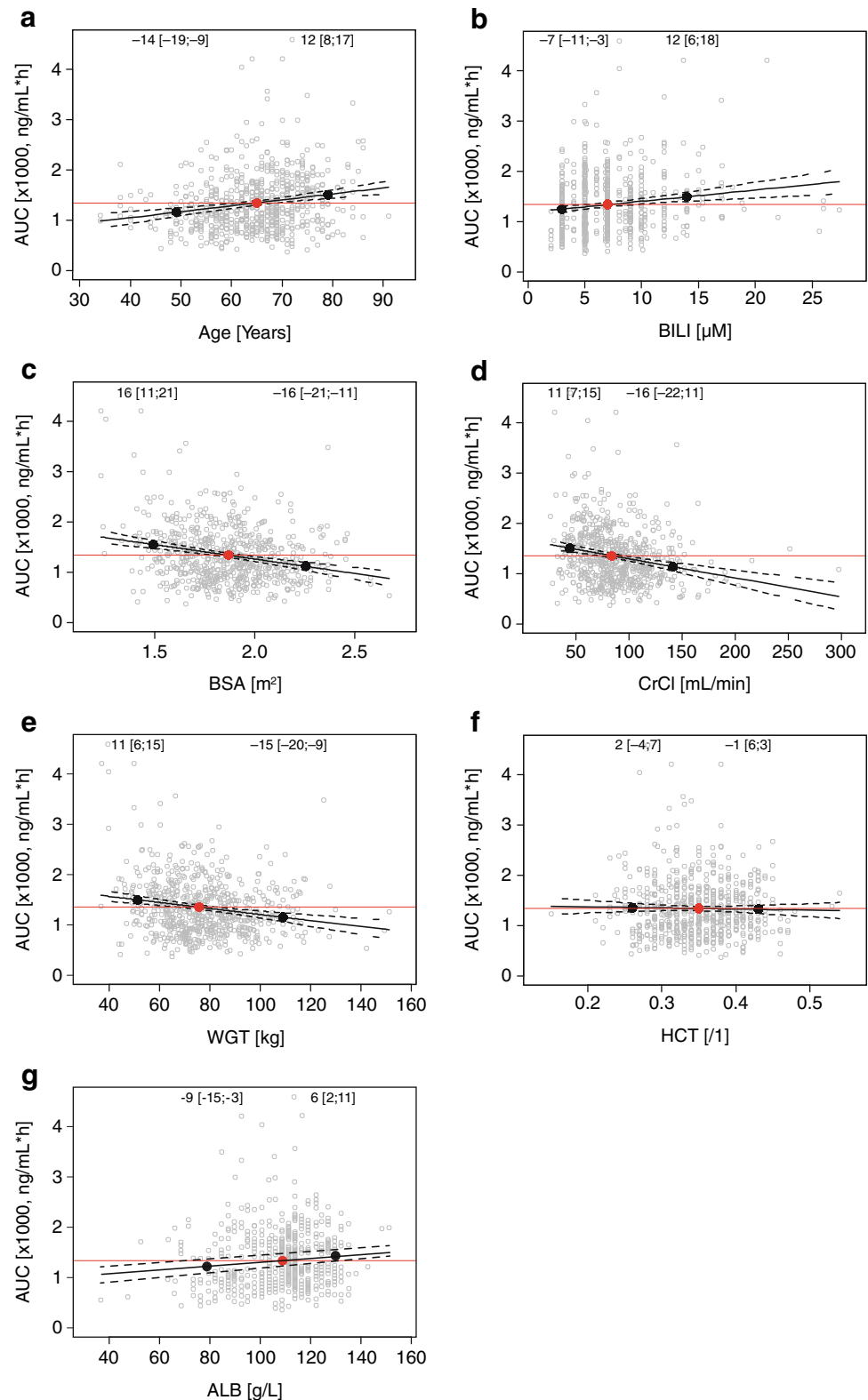
3.4 Model Simulation

The final population PK model was simulated to show the typical concentration–time profile following weekly treatment with oral ixazomib 4 mg in a 28-day treatment regimen (dosing on days 1, 8 and 15). All model parameters were set to the respective typical values with V_4 normalised to the median of individual BSA values reported in the analysis dataset (1.88 m²). Figure 6 shows the simulated concentration–time profile for a typical patient during the first two treatment cycles.

4 Discussion

This population PK analysis of the oral proteasome inhibitor ixazomib provides comprehensive model-based integration of data from 755 patients from ten ixazomib clinical trials, including seven phase I studies, two phase I/II studies and one phase III study. The final developed model consisted of a three-compartment structure; oral absorption was described as a first-order linear process with

Fig. 4 Correlations between key continuous covariates and individual predicted exposure in patients receiving oral ixazomib. Red and black dots indicate the median and 5th and 95th percentile of individual covariate values, respectively. Numbers (brackets) show the percent change in AUC_{∞} at the 5th and 95th percentile relative to the value at the median, based on the shown linear regression (and 95% CI). *ALB* serum albumin, *AUC* area under the concentration–time curve, *BILI* total bilirubin, *BSA* body surface area, *CrCl* creatinine clearance, *HCT* hematocrit, *WGT* weight



an estimated lag time, while distribution and elimination kinetics were linear. Patient-specific random effects were included on CL, F and V_4 . An off-diagonal variance–covariance matrix element representing the correlation

between random effects on CL and F was estimated, resulting in considerable improvement in model fit, and indicating a substantial correlation between these two random effects (82%). BSA on V_4 was the only patient

Fig. 5 Individual predicted exposure stratified by key categorical patient covariates for patients receiving oral ixazomib. Red and black dots indicate the mean exposure in the most prevalent category and in other categories, respectively. Numbers (brackets) in the top of plots show the percent change in AUC_{∞} (with 95% CI) in other categories relative to the most prevalent category, while numbers at the bottom show patients in each category. AUC area under the concentration–time curve, CI confidence interval, *len/dex* lenalidomide/dexamethasone

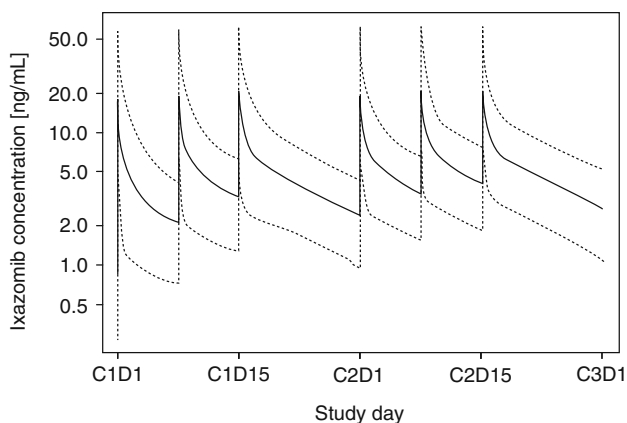
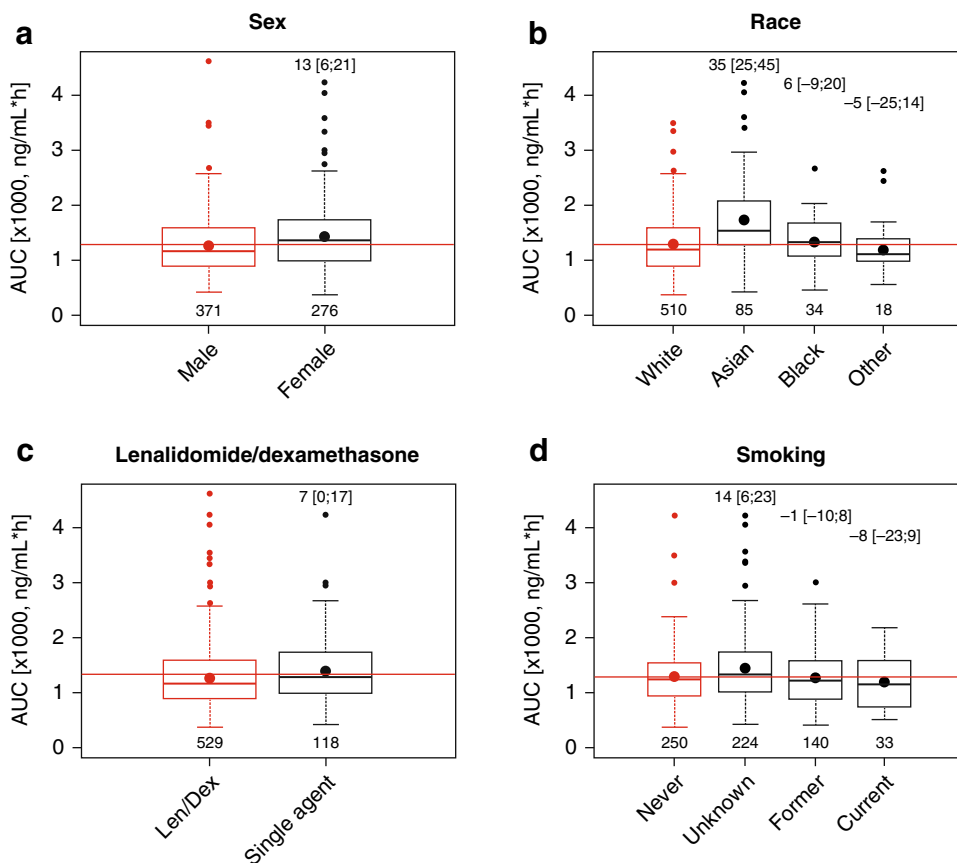


Fig. 6 Typical concentration–time profile (and 5th–95th percentile interval of individual predicted profiles) during the first two treatment cycles following oral dosing of ixazomib capsules at 4 mg on days 1, 8 and 15 of 28-day treatment cycles, based on a typical patient (body surface area = 1.88 m²)

covariate included in the final model. None of the other patient covariates tested including BSA, sex, age, race, mild or moderate renal impairment, mild hepatic impairment, smoking status and CYP1A2-modulatory drugs were found to impact CL, suggesting that no dose adjustment is required based on these covariates.

The results presented here are consistent with the previously published population PK analysis of ixazomib, which pooled data from four phase I studies available at the time [13]. In that analysis, ixazomib pharmacokinetics were described by a three-compartment model with first-order absorption and elimination. The estimated absolute bioavailability of ixazomib was 60%, and a small effect of BSA was observed on V_4 . The analysis supported a switch from BSA-based to fixed ixazomib dosing without modifications for mild/moderate renal impairment or age. In the present analysis, patients were treated with BSA-based ixazomib doses in studies C16001, C16002, C16003, C16004 and C16005 (phase I part), and fixed ixazomib doses in studies C16005 (phase II part), C16007, C16008, TOURMALINE-MM1, C16013 and TB-MC010034. The present analysis included an additional 529 patients as compared with the previous analysis, and 347 patients were from the phase III TOURMALINE-MM1 study.

Importantly, whereas the first population PK analysis only included studies conducted in the USA/Canada, the present analysis is global in scope, and was inclusive not only of Western, but also Asian patient populations. BSA had a small effect on V_4 , but did not impact CL; thereby confirming the results of the previous population PK analysis and further supporting the use of fixed ixazomib

dosing. The increased availability of patient level data for the present analysis provided an opportunity to formally evaluate relationships between PK parameters and covariates such as age, baseline bilirubin and creatinine clearance (CrCl) over a wide range of data that included a phase III study and two studies enrolling East Asian patients.

Consequently, the results of the present analysis have additional important implications for the further clinical development of ixazomib and represent pivotal integration of the ixazomib clinical PK database in support of regulatory review and labelling. Age over the range of 23–91 years was not found to have a clinically relevant effect on ixazomib PK parameters, suggesting that no dose adjustments are necessary for elderly patients. This is an important consideration given that the incidence of MM is highest in the elderly [27] and the median age at diagnosis is approximately 69 years [28]. Consistent with the previously published population PK analysis [13], neither CrCl nor total bilirubin had any clinically relevant impact on ixazomib pharmacokinetics, suggesting that no dose adjustments are necessary in patients with mild or moderate renal impairment (CrCl 30–90 mL/min) or patients with mild hepatic impairment (total bilirubin 1–1.5 times the upper limit of normal).

Given that there is a high prevalence of renal impairment in patients with MM [29], a phase I study to assess the pharmacokinetics of ixazomib in patients with severe renal impairment (CrCl < 30 mL/min), including patients with end-stage renal disease requiring dialysis, has been conducted and supports a reduced ixazomib dose of 3 mg in this patient population [11]. Additionally, a phase I study to assess the pharmacokinetics of ixazomib in patients with moderate or severe hepatic impairment (defined as per the National Cancer Institute Organ Dysfunction Working Group criteria) also demonstrated that these patients should receive a reduced dose of 3 mg [12].

Despite the modestly higher AUC in Asian patients (35%), exposures achieved after a 4-mg weekly dose are not expected to exceed those observed at the maximum tolerated dose in Western patients (5.5 mg). Additionally, adverse events following ixazomib treatment are reversible and manageable through dose modification guidelines; hence, no prospective starting dose adjustment is proposed for Asian patients, including Japanese patients. This is also consistent with the PK and safety study conducted in Asian patients in which a 4-mg dose was identified as the recommended phase II/III dose [30].

One of the attributes of this population PK analysis was estimation of absolute bioavailability using PK data collected after IV ($n = 108$ patients) and oral ($n = 647$ patients) administration, instead of conducting a dedicated two-way, crossover absolute bioavailability study as required by some regulatory agencies [31]. Use of this

model based approach in lieu of a dedicated absolute bioavailability study was accepted by the Australian Government Therapeutic Goods Administration [3].

This population PK analysis included data from patients who received ixazomib as a single agent as well as in combination, allowing the administration in combination with lenalidomide-dexamethasone to be tested as a categorical covariate. There were no alterations in ixazomib pharmacokinetics during combination treatment with lenalidomide-dexamethasone. This is an important finding because ixazomib is approved in combination with lenalidomide-dexamethasone for relapsed/refractory MM. Together with the clinical safety data [5], these results support the continued investigation of ixazomib in combination and as monotherapy in the ongoing phase III clinical trials.

Covariates describing the effect of CYP1A2- and CYP3A4-modulatory concomitant drugs were included in the analysis dataset as time-dependent categorical covariates describing the strongest (most inhibiting or inducing) CYP interaction on each patient-day [32]. Based on covariate analysis, both CYP1A2- and CYP3A4-modulatory drugs, had no statistically significant effect on ixazomib pharmacokinetics. However, it should be noted that a limitation of this aspect of the covariate analysis was that the fraction of records in the analysis dataset that were potentially affected by the CYP-modulatory concomitant drug categories evaluated was very low (1.4 and 3.7% for CYP1A- and CYP3A-modulatory drugs, respectively). Nevertheless, taken together with the established absence of an effect of the strong CYP3A inhibitor clarithromycin on ixazomib pharmacokinetics demonstrated in a controlled phase I clinical study, and the limited contribution of CYP enzymes to the total CL of ixazomib at clinically relevant concentrations [2], these results are consistent with, and support, the conclusion of low risk for clinically relevant drug–drug interactions between ixazomib and co-administered CYP-inhibitory drugs. It should however be noted that the strong pleiotropic PXR-mediated inducer rifampin produced a 74% decrease in systemic exposure (AUC) of ixazomib, likely reflecting an increased contribution of inducible enzymes/disposition mechanisms to the overall CL in the induced state. Accordingly, co-administration of ixazomib with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine and St. John's Wort) is not recommended [2].

5 Conclusions

Overall, these results demonstrate how population modeling and simulation can be pivotal in integrating PK knowledge and characterizing sources of variability in

systemic exposure, to inform posology decisions and labeling in oncology drug development. Results from this analysis were included in the US Prescribing Information and the European Summary of Product Characteristics for ixazomib.

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Compliance with Ethical Standards

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Conflict of Interest NG, MJH, DB, HvdV and KV are employed by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. PMD is an employee of Quantitative Solutions and contributed as a paid consultant to Millennium Pharmaceuticals, Inc., Cambridge, MA, USA. RDH's institution received grants for research funding for clinical trial conduct and RDH received an honorarium from Takeda for participating in an advisory board.

Ethics Approval All procedures performed in studies involving human participants were in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and appropriate regulatory requirements.

Consent to Participate All patients provided signed informed consent.

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