CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208462Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review	
NDA/SDN	NDA 208462 / SDN 1 \\Cdsesub1\evsprod\NDA208462
Type/Category	NME (Expedited), orphan drug designation
Brand Name	NINLARO
Generic Name	Ixazomib
Receipt Date	Part 1: July 10, 2015 Part 2: August 7, 2015
PDUFA Date	March 10, 2016
Proposed Indication	Treatment of patients with multiple myeloma who have received at least one prior therapy
Dosage Form	Capsules (4.0, 3.0, 2.3 mg)
Route of Administration	Oral
Dosing Regimen and Strength	4 mg taken orally on Days 1, 8 and 15 of a 28-day cycle
Applicant	Millennium Pharmaceuticals, Inc.
OND Division	Division of Hematology Products (DHP)
OCP Divisions	Division of Clinical Pharmacology V (DCPV) Division of Pharmacometrics (DPM)
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1 EXECUTIVE SUMMARY

Ixazomib is a small molecule inhibitor of the 20S proteasome. The sponsor is seeking approval of ixazomib for the treatment of patients with multiple myeloma who have received at least one prior therapy. The proposed dosing regimen is 4 mg orally on Days 1, 8, 15 of a 28-day cycle, to be administered in combination with lenalidomide and dexamethasone (LenDex).

The consideration for approval is based on the findings of the Phase 3 study where the safety and efficacy of Ixazomib+LenDex vs. Placebo+LenDex were compared in patients with relapsed/refractory multiple myeloma (n=722). The primary endpoint was progression-free survival (PFS) assessed by an Independent Review Committee. Treatment with Ixazomib+LenDex resulted in a median PFS improvement of 4 months (20.0 months vs. 15.9 months, hazard ratio 0.82 [95% CI: 0.67, 1.0]). The Phase 3 data showed no Exposure-Response (E-R) relationship for efficacy. However, E-R relationships for safety (thrombocytopenia, rash, gastrointestinal (GI) toxicities including diarrhea) were observed. These E-R relationships for safety support dose modifications in patients who experience thrombocytopenia, rash or GI toxicities including diarrhea. In addition, the E-R analyses for safety support reduced starting dose for patients with severe renal impairment/ESRD dialysis (3 mg), moderate or severe hepatic impairment (3 mg).

Ixazomib is rapidly absorbed (T_{MAX} ~1 hr) with an estimated absolute bioavailability of 58%. In mass balance evaluation, mean total recovery was 84% of administered dose, of which 62% recovered in urine (3.3% as unchanged drug) and 22% recovered in feces. Hepatic and renal impairment studies showed that ixazomib systemic exposure was increased by 13-42% in patients with moderate or severe hepatic impairment and those with severe renal impairment or end stage renal disease requiring dialysis compared to patients with normal hepatic and renal functions.

In vitro and clinical studies were conducted to characterize the metabolism and drug-drug interaction potential of ixazomib. In vitro studies indicate that both non-CYP and CYP enzymes may contribute to ixazomib metabolism. Clinical DDI studies with strong CYP3A4 inhibitors ketoconazole and clarithromycin did not show clinically meaningful effects on ixazomib systemic exposure. On the other hand, clinical study with the strong CYP3A4 inducer rifampin showed significant decrease in ixazomib exposure (AUC ↓74%, C_{MAX} ↓54%).

The submitted NDA data support the approval of ixazomib for the proposed patient population at the proposed dosing regimen.

1.1 RECOMMENDATIONS

NDA 208462 is acceptable for approval from a clinical pharmacology perspective provided that the sponsor and the FDA come to an agreement regarding the labeling language.

Decision	Acceptable to OCP?			Comment
Overall	Yes ☒	No ☐	NA ☐	
Evidence of Effectiveness	Yes ☒	No ☐	NA ☐	Based on Phase 3 Study C16010.
Proposed dose for general population	Yes ☒	No ☐	NA ☐	4 mg orally on Days 1, 8, 15 of a 28-day cycle.
Proposed dose selection for others	Yes ☒	No ☐	NA ☐	Reduce starting dose to 3 mg in patients with renal impairment (severe or end-stage renal disease requiring dialysis) or hepatic impairment (moderate or severe).
Pivotal BE	Yes ☐	No ☐	NA ☒	
Labeling	Yes ☒	No ☐	NA ☐	

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1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

Ixazomib is a small molecule inhibitor of the 20S proteasome. The sponsor is seeking approval of ixazomib for the treatment of patients with multiple myeloma who have received at least one prior therapy. The proposed dosing regimen is 4 mg capsule taken orally on Days 1, 8, 15 of a 28-day cycle, to be administered in combination with standard lenalidomide and dexamethasone (LenDex) therapy for multiple myeloma.

Dose Selection
The sponsor evaluated twice-weekly (Days 1, 4, 8, 11 of a 21-day cycle) and once-weekly (Days 1, 8, 15 of a 28-day cycle) dosing regimens of single agent oral ixazomib in patients with relapsed/refractory multiple myeloma (R/R MM). At the maximum tolerated doses (MTDs), the following efficacy and safety profiles were observed:

Rates (%)	2.0 mg/m^2 (twice-weekly)	2.97 mg/m^2 (once-weekly)
Overall response	15	30
Grade 3+ adverse events	78	77
Grade 4+ adverse events	48	35
Treatment discontinuation	20	13

Based on the higher response rate and improved tolerability, the once-weekly dosing regimen was selected for evaluation in combination with LenDex in patients with newly diagnosed MM. In Phase 2 evaluation in MM patients, ixazomib dose of 2.97 mg/m^2 in combination with LenDex was not well tolerated. The recommended Phase 2 dose (RP2D) of ixazomib in combination with LenDex was determined to be 2.23 mg/m^2. During Phase 2 evaluations, the sponsor's population PK analysis determined that body size does not significantly influence the pharmacokinetics of ixazomib PK. Based on such finding, the sponsor transitioned the RP2D from 2.23 mg/m^2 to a fixed 4 mg dose. This conversion was made based on a typical adult surface area of 1.8 m^2.

The pivotal Phase 3 Study evaluated 4 mg ixazomib orally on Days 1, 8, 15 of a 28-day cycle in combination with LenDex in R/R MM patients who have had at least 1 prior therapy (n=722). Patients were randomized 1:1 into the Ixazomib+LenDex or the Placebo+LenDex arm. The primary endpoint was progression-free survival (PFS), as assessed by an Independent Review Committee. Based on the most recent interim analysis (2^{nd}, database lock on September 9, 2015), the Ixazomib+LenDex arm showed a 4-month median PFS advantage over the Placebo+LenDex arm (20.0 months vs. 15.9 months, hazard ratio 0.82 [95% CI: 0.67, 1.0]).

Exposure-Response (E-R) Relationships
The results of E-R analyses for efficacy did not show a relationship between ixazomib systemic exposure and clinical response or PFS. However, results of E-R analyses for safety showed significant relationships between ixazomib systemic exposure and select AEs (rash, thrombocytopenia, diarrhea) indicating that sponsor's recommendations of dose reduction to manage these adverse events are acceptable. Ixazomib systemic exposure was not found to be a significant predictor of time to first dose reduction (p-value =0.069).

ADME

The absolute bioavailability of ixazomib is estimated to be 58%. Following oral administration, ixazomib is rapidly absorbed with a median T_{MAX} of 1 hour. It is highly bound to human plasma proteins at 99% with a blood-to-plasma ratio of 10. Mass balance evaluation showed that approximately 62% and 22% of the radiolabeled dose were recovered, respectively, in the urine and feces. Of those in the urine, only 3% was recovered as the unchanged drug. Metabolite profiling from the mass balance study was not complete at the time of NDA submission. In vitro metabolism studies show non-CYP and CYP enzymes contribute to ixazomib metabolism. Ixazomib has a half-life of about 10 days and systemic clearance of 1.9 L/h with minimal renal clearance (6%). Based on population PK analysis, ixazomib is dose-proportional in the dose range of 0.2 to 10.6 mg.

Hepatic and Renal Impairment

No dose adjustment is needed for patients with mild hepatic impairment or mild/moderate renal impairment, based on population PK analyses of Phase 3 data. However, dose reductions to 3 mg are recommended in patients with moderate/severe hepatic impairment or severe renal impairment/end stage renal disease requiring dialysis, based on clinical studies showing ~13-42% systemic exposure increases in these groups.

Drug-Drug Interactions (DDIs)

The contribution of CYP enzymes in the biotransformation of ixazomib is 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8), 2C9 (<1%) at supra-therapeutic concentrations. Clinical DDI studies with strong CYP3A4 inhibitors ketoconazole (when accounting for period effect) and clarithromycin did not show clinically meaningful effects on ixazomib PK. However, clinical study with strong CYP3A4 inducer rifampin showed significant decrease in ixazomib exposure (AUC ↓74%, C_{MAX} ↓54%). To avoid sub-therapeutic ixazomib concentrations, concomitant use of strong CYP3A4 inducers should be avoided.

Ixazomib was not identified as a reversible or time-dependent inhibitor or inducer of CYP enzymes or any major drug transporters. It was identified as a low affinity substrate of P-gp transporter.

2 QUESTION-BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Ixazomib is the biologically active boronic acid form of ixazomib citrate. The prodrug ixazomib citrate hydrolyzes rapidly and completely upon physiological conditions (across pH range of 1.6 to 7.4) to ixazomib. The equilibrium reaction and associated physical/chemical properties for ixazomib citrate and ixazomib are shown in **Figure 1**.

Figure 1. Ixazomib citrate – Ixazomib reaction and associated physical/chemical properties.
(Source: Sponsor's M 2.2 Introduction, Figure 1.a)

Ixazomib is available as immediate-release capsules (4.0, 3.0, 2.3 mg).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ixazomib is a selective and reversible proteasome inhibitor. It preferentially binds and inhibits the chymotrypsin-like activity of the β5 site (IC_{50} = 3.4 nM), and to a lesser extent β1 (IC_{50} = 31 nM) and β2 (IC_{50} = 3500 nM), of the 20S proteasome. Inhibition of the 20S proteasome leads to the disruption of cellular regulatory mechanisms which ultimately result in the activation of apoptotic pathways and cell death.

The proposed indication is for the treatment of patients with multiple myeloma who have received at least one prior therapy.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage and administration is 4 mg taken orally on Days 1, 8 and 15 of a 28-day cycle. Ixazomib should be taken at least 1 h before or at least 2 h after food.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A list of relevant clinical pharmacology and clinical studies included in the ixazomib application is shown in **Table 1**.

Table 1. Summary of ixazomib clinical pharmacology and clinical studies

Study	Assessment	Design	Population	Dosing Regimen
C16001	IV characterization of PK and PD	Phase 1, FIH, open-label, dose escalation w/ MTD disease and tumor PD expansion	Non-hematologic malignancies (n=116, PK=35)	IV, BIW for 2 wks (Days 1, 4, 8, 11) in 21-day cycles. -Dose = 0.125-2.34 mg/m^2 Ixa -Expansion = 1.76 mg/m^2 Ixa
C16002	IV characterization of PK and PD	Phase 1, open-label, dose escalation and expansion	Lymphoma (n=31, PK=30)	IV, QW for 3 wks (Days 1, 8, 15) in 28-day cycles. -Dose = 0.125-3.11 mg/m^2 Ixa -Expansion = 2.34 mg/m^2 Ixa
C16003	PO monotherapy characterization of PK	Phase 1, open-label, dose escalation and expansion	R/R MM (n=60, PK=50)	PO, BIW for 2 wks (Days 1, 4, 8, 11) in 21-day cycles. -Dose = 0.24-2.23 mg/m^2 Ixa -Expansion = 2.0 mg/m^2 Ixa
C16004	PO monotherapy characterization of PK	Phase 1, open-label, dose escalation and expansion	R/R MM (n=60, PK=44)	PO, QW for 3 wks (Days 1, 8, 15) in 28-day cycles. -Dose = 0.24-3.95 mg/m^2 Ixa -Expansion = 2.97 mg/m^2 Ixa
C16007	PO monotherapy characterization of PK	Phase 1, open-label, dose escalation and expansion	R/R AL that requires active treatment (n=27, PK=22)	PO, QW for 3 wks (Days 1, 8, 15) in 28-day cycles. -Dose = 4, 5.5 mg Ixa -Expansion = 4 mg Ixa
C16005	PO combination with LenDex, characterization of PK	Phase 1/2, open-label, induction & maintenance, dose escalation and RP2D	ND MM (n=65, PK=11)	**Induction (12 cycles):** QW for 3 wks (Days 1, 8, 15) + 25 mg Len (Days 1-21) + 40 mg Dex (Days 1, 8, 15, 22) in 28-day cycles. -Dose = 1.68-3.95 mg/m^2 Ixa (MTD = 2.97 mg/m^2) -RP2D = 4.0 mg Ixa fixed (equivalent to 2.23 mg/m^2) **Maintenance (≥13 cycles):** Continue Ixa as monotherapy QW for 3 wks (Days 1, 8, 15) in 28-day cycles.
C16008	PO combination with LenDex, characterization of PK	Phase 1/2, open-label, induction & maintenance, dose escalation and RP2D	ND MM (n=64, PK=14)	**Induction (16 cycles):** BIW for 2 wks (Days 1, 4, 8, 11) + 25 mg Len (Days 1-14) + Dex (Days 1, 2, 4, 5, 8, 9, 11, 12) at 20 mg (Cycles 1-8) or 10 mg (Cycles 9-16) in 21-day cycles. -Dose = 3, 3.7 mg Ixa -RP2D = 3 mg Ixa **Maintenance (≥17 cycles):** Continue Ixa as monotherapy BIW for 2 wks (Days 1, 4, 8,

				11) in 21-day cycles.
C16010	PO combination with LenDex, population PK and E-R analyses	Phase 3, randomized, double-blind, placebo controlled	R/R MM (n=722, PK=sparse)	4 mg Ixa QW or placebo QW for 3 wks (Days 1, 8, 15) + 25 mg Len (Days 1-21) + 40 mg Dex (Days 1, 8, 15, 22) in 28-day cycles.
C16009	DDI, food effect and relative BA	Phase 1, multi-center, sequential, 5-arms: -Arm 1: ketoconazole DDI (n=29, PK=16) -Arm 2: relative BA (n=20, PK=14) -Arm 3: food effect (n=24, PK=15) -Arm 4: rifampin DDI (n=18, PK=14) -Arm 5: clarithromycin DDI (n=21, PK=15)	Advanced non-hematologic malignancies or lymphoma (n=112, PK=76)	**Cycle 1 (28 days unless otherwise noted):** -Arm 1: 2.5 mg Ixa (Days 1, 15) + 400 mg ketoconazole (Days 12-25) -Arm 2: 4 mg Ixa (Days 1, 15) crossover study of Capsule A and B -Arm 3: 4 mg Ixa (Days 1, 15) crossover study of fasted and fed -Arm 4: 4 mg Ixa (Day 8) + 600 mg rifampin QD (Days 1-14) in 21-day cycle -Arm 5: 2.5 mg Ixa (Day 6) + 500 mg clarithromycin BID (Days 1-16) in 21-day cycle **Cycles ≥ 2 (all arms):** 4 mg Ixa QW for 3 wks (Days 1, 8, 15) in 28-day cycles.
C16016	Mass Balance/ADME	Phase 1, 2-part, open-label	Advanced solid tumors or lymphoma (n=7, PK=5)	**Part A (PK):** Oral solution of 4 mg [^{14}C] Ixa containing ~500 nCi total radioactivity (Day 1) + 4 mg Ixa capsule (Days 14, 21) in 35-day period. **Part B (optional):** 4 mg Ixa capsule QW (Days 1, 8, 15) in 28-day cycles.
C16015	Renal impairment (severe and ESRD on dialysis)	Phase 1b, open-label, multi-center	R/R MM with the following (n=41, PK=38): -normal renal function -severe RI -ESRD requiring hemodialysis	**Part A (PK):** 3 mg Ixa SD (Day 1) in 15-day period. **Part B (optional):** 4 mg Ixa (or lower if Part A dose not tolerated) QW for 3 wks (Days 1, 8, 15) + 40 mg

				Dex (optional, Days 1, 8, 15, 22) in 28-day cycles.
C16018	Hepatic impairment (moderate or severe)	Phase 1, open-label, multi-center	Advanced solid tumors or hematologic malignancies (n=48, PK=43) with the following: -normal hepatic function -moderate HI -severe HI	**Part A (PK):** 4 mg (normal hepatic), 2.3 mg (moderate HI), or 1.5 mg (severe HI) Ixa SD (Day 1) in 15-day period. **Part B (optional):** Ixa QW at Part A dose (with possible escalation) for 3 wks (Days 1, 8, 15) in 28-day cycles.
C16013	PO combination with LenDex, PK in Asians	Phase 1, open-label, dose confirmation	Asians with R/R MM (n=43, PK=24)	4 mg Ixa QW for 3 wks (Days 1, 8, 15) + 25 mg Len (Days 1-21) + 40 mg Dex (Days 1, 8, 15, 22) in 28-day cycles.
TB-MC010034	PO monotherapy or combination with LenDex, PK in Japanese	Phase 1, open-label	Japanese with R/R MM (n=14, PK=14, 7 each in monotherapy or combination)	**Monotherapy:** 4 mg Ixa QW for 3 wks (Days 1, 8, 15) in 28-day cycles. **Combination with LenDex:** 4 mg Ixa QW for 3 wks (Days 1, 8, 15) + 25 mg Len (Days 1-21) + 40 mg Dex (Days 1, 8, 15, 22) in 28-day cycles.

IV = intravenous, PO = oral, PK = pharmacokinetics, PD = pharmacodynamics, Ixa = ixazomib, Len = lenalidomide, Dex = dexamethasone, LenDex = lenalidomide + dexamethasone, FIH = first-in-human, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose, SD = single dose, R/R = relapsed and/or refractory, ND = newly diagnosed, MM = multiple myeloma, AL = systemic light chain amyloidosis, RI = renal impairment, ESRD = end-stage renal disease, HI = hepatic impairment, DDI = drug-drug interaction, BA = bioavailability, E-R = exposure-response, ADME = absorption, distribution, metabolism, excretion, QW = once weekly, BIW = twice weekly, QD = once daily, BID = twice daily

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint in the registration Study C16010 was progress-free survival (PFS), defined as the time from randomization date to the first documented date of disease progression based on central laboratory results and International Myeloma Working Group (IMWG) criteria as evaluated by an Independent Review Committee (IRC), or death due to any cause, whichever occurred first. Additional outcome measures included overall survival (OS), overall response rate (ORR), duration of response (DOR) and time to progression (TTP).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, ixazomib was the major component in human plasma after oral administration and it was appropriately identified and measured to assess PK parameters (refer to **Section 2.6**).

2.2.4 Exposure-response

2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

There were no significant ixazomib exposure-response (E-R) relationships for efficacy including the primary endpoint of PFS **(Figures 20 and 21 in Section 3.1)** or complete response within the exposure range observed in patients with R/R MM who completed at least 1 prior therapy. The studied start dose of 4 mg is one dose level lower than the MTD (5.5 mg corresponding to 2.97 mg/m^2 for a typical patient) and data do not indicate that increasing ixazomib exposure would offer any additional benefit. In addition, the baseline risk factors among the four exposure quartiles seem to be reasonably balanced and there were no relationships between baseline risk factors and exposures. The analysis was repeated with 2^{nd} interim data for PFS and no significant effect of ixazomib exposure on PFS was observed with the data either. Refer to Pharmacometrics Review for details (see **Section 3.1**).

2.2.4.2 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

Significant E-R relationships for safety were observed for major adverse events including Grade 3+ thrombocytopenia, Grade 2+ rash and Grade 2+ gastrointestinal toxicities (see **Figure 2** for thrombocytopenia and rash). Detailed dose modification schemes are proposed for thrombocytopenia and rash, and dose adjustment for severe nausea, vomiting and/or diarrhea is indicated in Warning and Precautions for gastrointestinal toxicities. Sponsor's proposed dose reductions for these adverse events are acceptable. However, more detailed dose modification for gastrointestinal toxicities is recommended. Refer to Pharmacometrics Review for details (see **Section 3.1**).

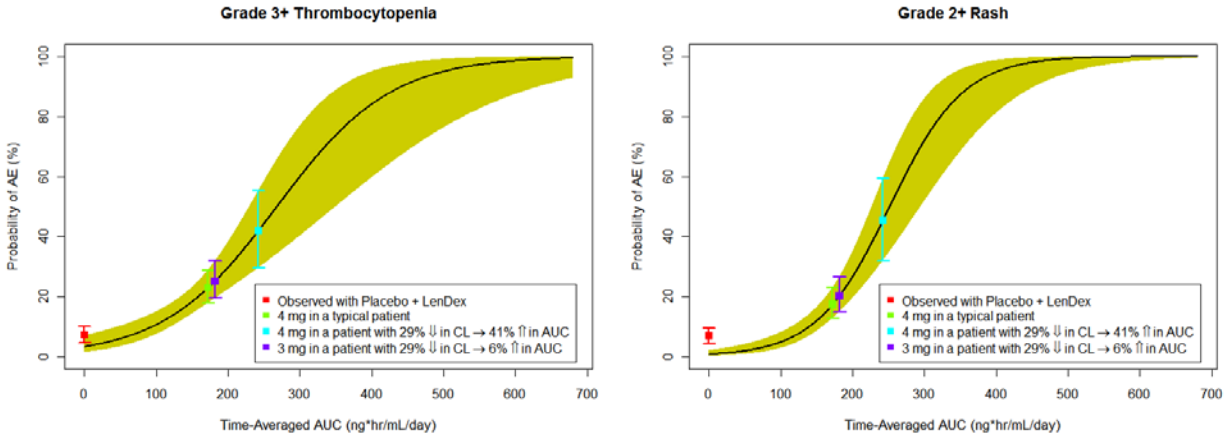


Figure 2. Probability of thrombocytopenia (left) and rash (right) vs. ixazomib daily AUC.
(Source: Pharmacometrics Review, Section 3.1)

2.2.4.3 *Does this drug prolong the QT or QTc interval?*

A population concentration-QTc analysis was conducted with PK and ECG data from 2 IV studies (C16002, C16002) and 2 PO studies (C16003, C16004) **(Table 2)**.

Table 2. Clinical studies included in the Ixazomib PK-QTc analysis

Study	Description	Treatment (Sample Size)[a]	Dosing Day in Cycle	ECG Extraction and Time-Matched PK Sample
C16001	Open-label, dose-escalation, in patients with advanced nonhematologic malignancies.	0.125 mg/m^2 (n=101)	1,4,8,11 21-Day Cycle	Schedule A: Day 1: 0 (predose), 5 min (postdose) Day 11: 0 (predose), 5 min, 1, 2 h Day 12: 0 (24 h from Day 11) Schedule B: Day 1: 0 (predose), 10 min (postdose) Day 11: 0 (predose), 5 min
C16002	Open-label, dose escalation study in adult patients with lymphoma	0.125 mg/m^2 (n=34)	1,8,15 28-Day Cycle	Day 1: 0 (predose), 5 min (postdose) Day 15: 0 (predose), 5 min
C16003	Open-label, dose escalation study in patients with relapsed and/or refractory multiple myeloma	0.24 mg/m^2 (n=70)	1,4,8,11 21-Day Cycle	Day 1: 0 (predose), 0.5, 1, 4 h (postdose) Day 2: 0 (24 h from Day 1 Dose) Day 11: 0 (predose), 0.5, 1, 4 h (postdose) Day 12: 0 (24 h from Day 11 Dose)
C16004	Open-label, dose escalation study in adult patients with relapsed and/or refractory multiple myeloma	0.24 mg/m^2 MTD from C16004 (n=70)	1,8,15 28-Day Cycle	Day 1: 0 (predose), 0.5, 1, 4 h (postdose) Day 15: 0 (predose), 0.5, 1, 4 h (postdose) Day 16: 0 (24 h from Day 15 Dose)

[a]Anticipated sample size
h = hour; min = minute; mg/m^2 = milligram per meter squared; PK = pharmacokinetic
(Source: QT-IRT review finalized 06/03/2014 in DARRTS, Table 2)

A previous QT-IRT review did not find clear dose- or exposure-QTc relationship for ixazomib. Refer to posted QT-IRT review in DARRTS for details (J. Liu, finalized 06/03/2014).

2.2.4.4 ***Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?***

Based on the currently available data, the proposed dosing regimen of 4 mg ixazomib on Days 1, 8, 15 of a 28-day cycle in combination with LenDex appears acceptable for the treatment of patients with (b) (4) MM who have received at least 1 prior therapy.

The proposed starting dose/dosing regimen is 4 mg ixazomib taken orally on Days 1, 8, and 15 of a 28-day cycle, to be administered in combination with standard LenDex therapy (lenalidomide: 25 mg on Days 1-21, Dexamethasone: 40 mg on Days 1, 8, 15, 22) for the treatment of patients with multiple myeloma who have had at least one prior therapy.

In Phase 1 studies, both twice-weekly (Study C16003: ixazomib on Days 1, 4, 8, 11 of a 21-day cycle) and once-weekly regimens (Study C16004: ixazomib on Days 1, 8, 15 of a 28-day cycle) of single agent oral ixazomib were evaluated in patients with R/R MM. At the maximum tolerated dose (MTD) expansion cohorts (2.0 mg/m^2 for twice-weekly, 2.97 mg/m^2 for once-weekly), both regimens achieved similar rates of Grade 3+ adverse events (77% vs. 78%), however, the once-weekly regimen had higher response rate (30% vs. 15%) and lower rates of Grade 4+ adverse events (35% vs. 48%) and treatment discontinuation (13% vs. 20%). Due to the higher response rate and improved tolerability, the once-weekly dosing schedule was selected over the twice-weekly schedule for evaluation with LenDex combination therapy in patients with newly diagnosed MM (Phase 1-2 Study C16005). In Study C16005, in general, there was a trend of higher rates of adverse events (Grade 3+ adverse events, serious adverse events, dose reductions, and treatment withholding and discontinuation) with higher ixazomib doses. The MTD in combination with LenDex was determined to be 2.97 mg/m^2, this dose was however observed to compromise the dose intensity for lenalidomide (85% lenalidomide dose intensity at 2.97 mg/m^2 MTD vs. 96% lenalidomide dose intensity at 2.23 mg/m^2 dose). In summary, the 4 mg ixazomib (equivalent to 2.23 mg/m^2) once-weekly dose in combination with LenDex was selected for further evaluation for following reasons:

- Once-weekly regimen: higher response rate and improved tolerability compared to twice-weekly regimen
- 2.23 mg/m^2 dose : improved safety/tolerability profile and allowed for preservation of lenalidomide dose intensity
- Fixed dose: lack of a clinically meaningful effect of body size (body surface area or body weight) on ixazomib clearance, based on population PK analysis, to support body size-based dosing

Phase 3 Study C16010 evaluated 4 mg ixazomib on Days 1, 8, 15 of a 28-day cycle in combination with LenDex in R/R MM patients who have had at least 1 prior therapy (n=722). Patients were randomized 1:1 into the Ixazomib+LenDex or the Placebo+LenDex arm. The primary endpoint was progression-free survival (PFS), as assessed by an Independent Review Committee. Based on the most recent interim analysis (2nd, database lock on September 9, 2015), the Ixazomib+LenDex arm showed a 4-month median PFS advantage over the Placebo+LenDex arm (20.0 months vs. 15.9 months, hazard ratio 0.82 [95% CI: 0.67, 1.0]) **(Table 3)**.

Table 3. Phase 3 Study C16010 progression-free survival results

Progression-Free Survival	Ninlaro + LD (N=360)	Placebo + LD (N=362)
Patients with events, n (%)	177 (47.6)	195 (52.4)
Progression	158 (42.5)	180 (48.4)
Death	19 (5.1)	15 (4.0)
Median PFS (months) (95% CI)	20.0 (18.0, 23.4)	15.9 (13.2, 18.8)
Stratified HR(95% CI)	0.82 (0.67, 1.0)	
p-value	0.055	

(Source: FDA Biostatistics)

The results of E-R analyses for efficacy did not show a relationship between ixazomib systemic exposure and clinical response or PFS. However, results of E-R analyses for safety showed significant relationships (p-value < 0.05) between ixazomib systemic exposure and select AEs (rash, peripheral neuropathy, diarrhea, nausea, vomiting, fatigue, thrombocytopenia, anemia)—see **Section 2.2.4.2** for details. Ixazomib systemic exposure was not found to be a significant predictor of time to first dose reduction (refer to Pharmacometrics Review in **Section 3.1**).

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

Single- and multiple-dose PK of ixazomib have been evaluated in the clinical pharmacology studies listed in **Table 1**.

Single-Dose Monotherapy
Single-dose PK parameters from Renal Impairment Study C16015 and Hepatic Impairment Study C16018 are provided in **Table 4—**only control group patients (those with normal renal or hepatic function) are shown.

Table 4. Ixazomib PK parameters following single-dose oral administration in patients

PK Parameter	Study C16015 (3 mg, n=18)	Study C16018 (4 mg, n=12)
T_{MAX} (h)	1.04 (0.47-4.0)	0.95 (0.48-4.0)
C_{MAX} (ng/mL)	26 (56)	61 (54)
$AUC_{0\text{-}168h}$ (h·ng/mL)	347 (42)	846 (44)
$AUC_{0\text{-}LAST}$ (h·ng/mL)	575 (38)	1160 (41)

T_{MAX} values provided as median and range, others as geometric mean (%CV).

Multiple-Dose Monotherapy
Once-weekly dosing of ixazomib monotherapy in patients with R/R MM was evaluated in Study C16004. The ixazomib dose range evaluated was 0.24 to 3.95 mg/m^2 QW for 3 weeks in 28-day

cycles. Multiple-dose PK profile and parameters from this study are provided in **Figure 3** and **Table 5**.

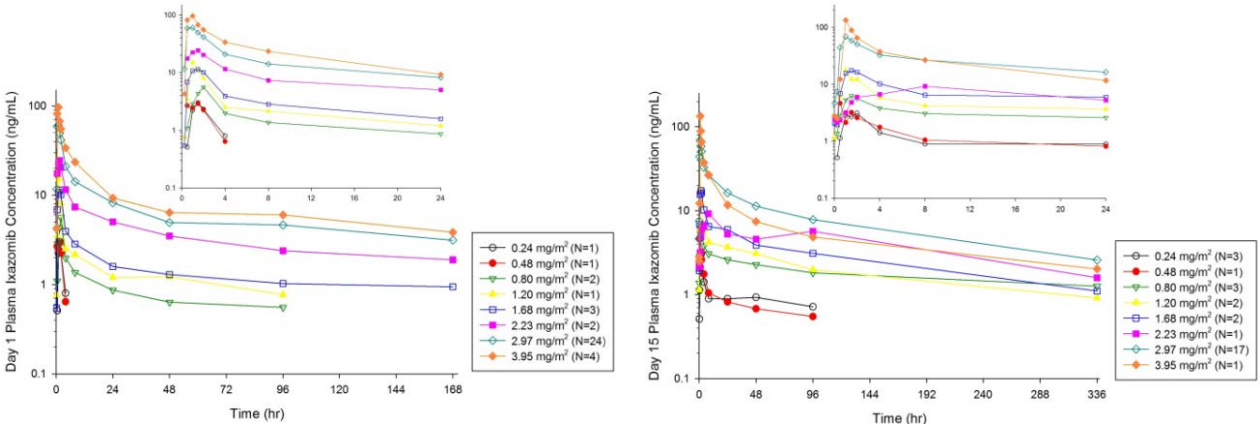


Figure 3. Day 1 (left) and Day 15 (right) ixazomib PK profile following once weekly monotherapy dosing in patients with R/R MM.
(Source: Sponsor's C16004 Clinical Study Report, Figures 11-1 and 11-2)

Table 5. Ixazomib PK parameters following multiple-dose oral administration in ixazomib monotherapy

	Ixazomib Dose (mg/m^2)							
Parameter	**0.24**	**0.48**	**0.8**	**1.2**	**1.68**	**2.23**	**2.97**	**3.95**
Day 1								
N	1	1	2	1	3	2	24[a]	4
T_{max} (hr)[a]	1.5	1.53	1.03, 2	1	1.52 (1-2)	1, 1.5	1 (0.5-4)	1 (0.533-1.5)
C_{max} (ng/mL)	3.01	2.91	2.84, 8.65	15.1	11.9 (70)	21.2, 36.9	69.8 (61)	98.1 (64)
AUC_{0-168} (ng•hr/mL)	NC	NC	NC	NC	192, 324	598	906 (49)	1180 (53)
DN C_{max} (ng/mL/mg)	6.02	3.64	2.03, 6.18	6.86	3.48 (70)	4.24, 8.58	12.0 (57)	12.5 (75)
DN AUC_{0-168} (ng•hr/mL/mg)	NC	NC	NC	NC	49.2, 95.3	139	161 (48)	151 (54)
Day 15								
N	3	1	3	2	2	1	17[b]	1
T_{max} (hr)[a]	1.07 (1-2)	0.5	1.83 (1-2)	1, 1	1, 1.53	8	1 (0.5-4.03)	1.03
C_{max} (ng/mL)	3.54 (26)	4.64	5.61 (74)	11.8, 24	8.65, 26.6	9.24	65.4 (61)	134
AUC_{0-168} (ng•hr/mL)	NC	NC	366, 431	NC	562, 764	868	1710 (53)	1460
DN C_{max} (ng/mL/mg)	10.4 (61)	5.8	4.01 (74)	6.56, 10.4	2.22, 7.82	2.15	11.3 (60)	20.3
DN AUC_{0-168} (ng•hr/mL/mg)	NC	NC	261, 308	NC	144, 225	202	288 (54)	221
$t_{1/2}$ (hr)	NC	NC	271	185, 196	180, 198	175	144 (39)	165
Accumulation Ratio for AUC_{0-168}	NC	NC	NC	NC	2.36, 2.92	1.45	2.12 (24)	1.19

Source: C16004 Table 11-1.
Abbreviations: AUC_{0-168}=area under the plasma ixazomib concentration-time curve from time 0 to 168 hours postdose; C_{max}=maximum observed plasma concentration; DN=dose normalized; N=number of patients; NC=not calculated; $t_{1/2}$=terminal half-life; T_{max}=time of C_{max}.
Parameters are presented as geometric mean (%CV), except for T_{max} which is presented as median (range). Individual values are reported if N<3.
a N=17 for AUC_{0-168} and DN AUC_{0-168}.
b N=11 for $t_{1/2}$, 10 for AUC_{0-168}, and DN AUC_{0-168} and 8 for the accumulation ratio.
(Source: Sponsor's C16004 Clinical Study Report, Table 11-1)

Multiple-Dose Combination Therapy w/ LenDex

Once-weekly dosing of ixazomib in combination with LenDex in patients with newly diagnosed MM was evaluated in Study C16005. The ixazomib dose range evaluated was 1.68 to 3.95 mg/m^2 QW for 3 weeks in 28-day cycles. Multiple-dose PK profile and parameters from this study are provided in **Figure 4** and **Table 6**.

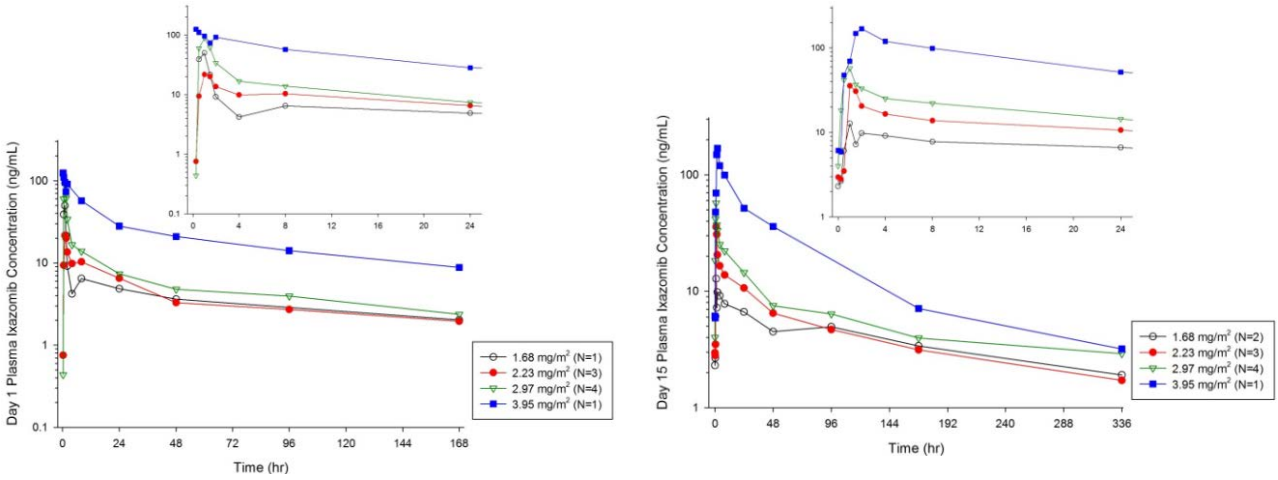


Figure 4. Day 1 (left) and Day 15 (right) ixazomib PK profile following once weekly combination dosing with LenDex in patients with newly diagnosed MM.
(Source: Sponsor's C16005 Clinical Study Report, Figures 11-1 and 11-2)

Table 6. Ixazomib PK parameters following multiple-dose oral administration in ixazomib combination therapy with LenDex

	Ixazomib Dose (mg/m^2)			
Parameters (Units)	**1.68**	**2.23**	**2.97**	**3.95**
Day 1				
N	1	3	4	1
T_{max} (hr)	1.02	1.52 (1-8)	1.06 (0.5-1.08)	0.25
C_{max} (ng/mL)	49.8	22.3 (52)	94.8 (34)	124
AUC_{0-168} (ng•hr/mL)	603	588 (54)	923 (17)	3550
DN C_{max} (ng/mL/mg)	13.8	6.10 (49)	17.0 (44)	13.8
DN AUC_{0-168} (ng•hr/mL/mg)	168	161 (61)	166 (17)	394
Day 15				
N	2	3	4[a]	1
T_{max} (hr)	1.05, 7.28	1 (0.983-2.03)	1.02 (1-2.02)	2
C_{max} (ng/mL)	6.76, 21.3	31.4 (82)	53.5 (39)	169
AUC_{0-168} (ng•hr/mL)	749, 930	1080 (10)	1830 (14)	5240
DN C_{max} (ng/mL/mg)	1.93, 5.92	8.57 (74)	9.62 (50)	20.6
DN AUC_{0-168} (ng•hr/mL/mg)	214, 258	296 (16)	341 (10)	639
$t_{1/2}$ (hr)	205, 216	157 (20)	178 (28)	84.7
Accumulation Ratio for AUC_{0-168}	1.54	1.85 (42)	2.05 (31)	NC

Source: C16005 Table 11-2.
Abbreviations: AUC_{0-168}=area under the plasma ixazomib concentration-time curve from time 0 to 168 hours postdose; C_{max}=maximum observed plasma concentration; DN=dose normalized; N=number of patients; NC=not calculated; $t_{1/2}$=terminal half-life; T_{max}=time of C_{max}.
Parameters are presented as geometric mean (%CV), except for T_{max} which is presented as median (range).
Individual values are reported if N<3.
a N=3 for AUC_{0-168}, DN AUC_{0-168}, and for the accumulation ratio.
(Source: Sponsor's C16005 Clinical Study Report, Table 11-2)

2.2.5.2 *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

Ixazomib is a cytotoxic agent. All clinical studies were conducted in cancer patients or those with systemic light-chain amyloidosis. Therefore, PK comparison between healthy subjects and patients cannot be conducted.

2.2.5.3 *What are the characteristics of drug absorption?*

Following oral administration, ixazomib is absorbed rapidly with an overall median T_{MAX} of 1 h. Following multiple-dose administration, plasma exposure of ixazomib generally increased dose proportionally over a dose range of 0.48 to 3.95 mg/m^2 (1.4 to 8.9 mg actual administered). Based on population PK analysis, no apparent relationship was observed between dose (0.2 to 10.6 mg) and oral clearance, supporting dose-linearity within this dose range. Absolute bioavailability was estimated to be 58% based on population PK analyses of IV and oral PK data.

2.2.5.4 *What are the characteristics of drug distribution?*

Based on population PK modeling, the volume of distribution at steady state was estimated to be 543 L. Ixazomib is highly bound to plasma proteins, mainly albumin, at 99%. Plasma protein binding was not found to be affected by organ impairment (renal or hepatic) status. Ixazomib distributes into red blood cells with a blood/plasma ratio of approximately 10, which appears consistent with its mechanism of action against 20S proteasomes in red blood cells.

2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

In Study C16016, the mass balance of ixazomib was assessed in 7 patients with advanced or metastatic solid tumor or lymphoma. A single dose of 4.1 mg [^{14}C]-ixazomib oral solution was administered to patients. Blood samples for ixazomib plasma PK and total radioactivity and metabolite profiles were collected over a 35-day period. Samples in urine and feces were collected post-dose continuously for 8-days and then intermittently for up to 35 days. The mean total recovery of administered dose was 84% with 62% of the dose recovered in urine (3.3% as unchanged drug) and 22% of the dose recovered in feces **(Figure 5)**. Metabolite profiling was not complete at the time of NDA submission.

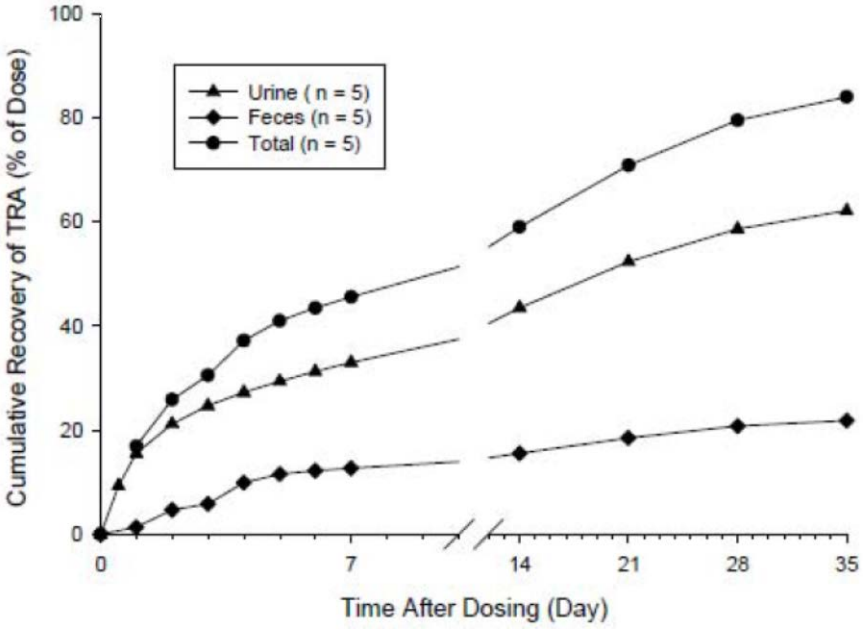


Figure 5. Mean cumulative percent of radioactive dose recovered in urine and feces after a single oral solution dose of 4.1 mg [14C]-ixazomib in patients.
(Source: Sponsor's C16016 Clinical Study Report, Figure 11.c)

2.2.5.6 *What are the characteristics of drug metabolism?*

The sponsor claims that non-CYP-mediated metabolism of ixazomib occurs at clinical concentrations (0.1 and 0.5 µM, similar to concentrations following 4 mg ixazomib oral administration) while CYP-mediated metabolism occurs at supra-therapeutic concentration (10 µM). This was based on in vitro CYP P450 phenotyping results (Report MLN9708-31259) in which the rates of ixazomib disappearance and metabolite formation were similar in control incubations with or without active CYP enzymes. At supra-therapeutic concentration, the contribution of CYP-mediated metabolism is as follows: 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8), 2C9 (<1%).

The metabolic pathway of ixazomib is in shown in **Figure 6**. Oxidative deboronation of ixazomib to hemiaminal metabolite (M1) is the major biotransformative pathway evidence in all species including humans. Metabolite profiling from this study was not complete at the time of NDA submission.

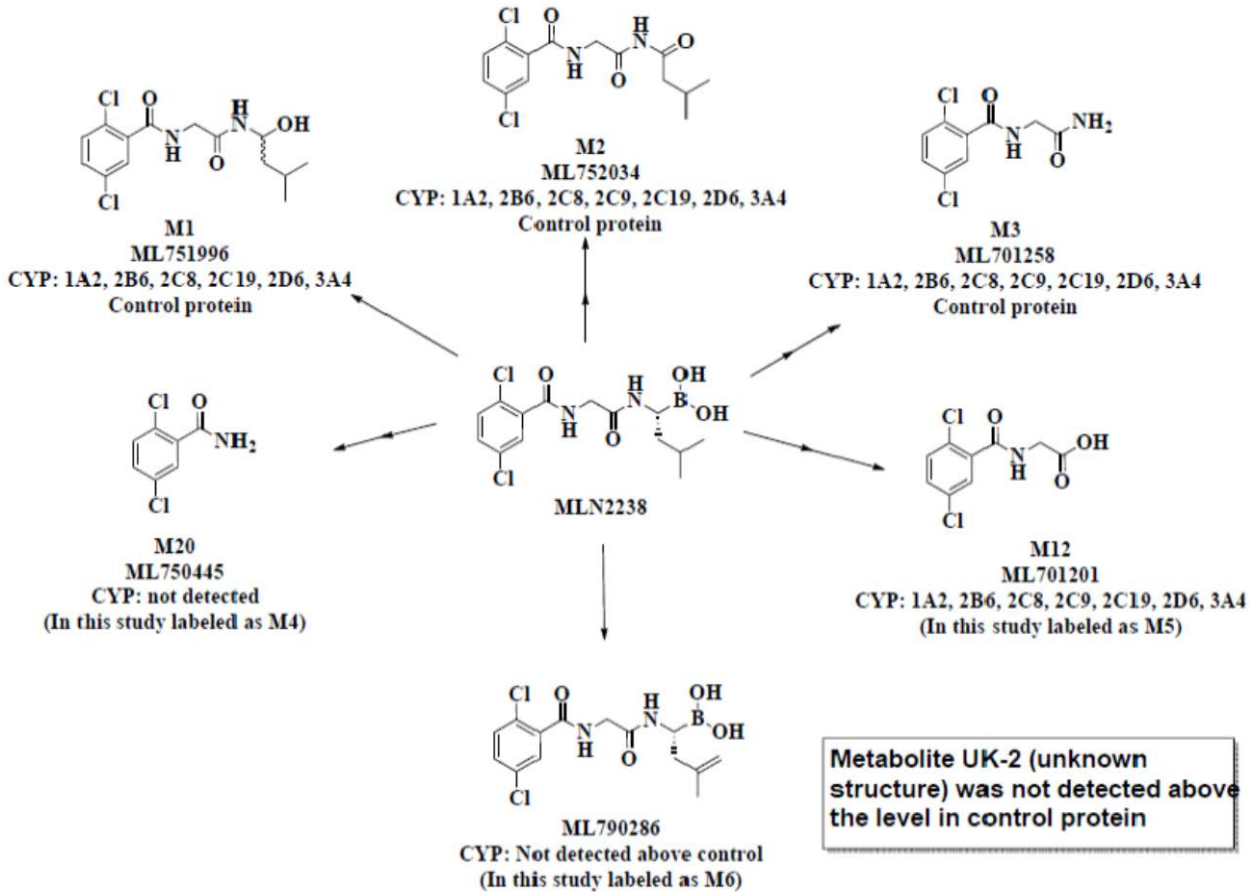


Figure 6. Metabolic pathway of ixazomib.
(Source: Sponsor's Report MLN9708-31259, Figure 1)

2.2.5.7 *What are the characteristics of drug excretion?*

The mass balance study (C16016) showed that the mean total recovery of 4.1 mg [^{14}C]-ixazomib was 84% with 62% of the dose recovered in the urine (3.3% as unchanged drug) and 22% recovered in the feces. It indicated that most of the drug recovered in the urine is in the form of metabolites.

Elimination

Based on population PK analysis, plasma clearance of ixazomib is 1.86 L/h (apparent clearance is 3.21 L/h, based on oral bioavailability of 58%) and the geometric mean terminal half-life is 9.5 days. Based on mass balance study (C16016), renal clearance was observed to be 0.07 L/h and 0.06 L/h for Day 1 and 15, respectively.

2.2.5.8 *Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?*

Following multiple-dose administration, plasma exposure of ixazomib generally increased dose proportionally over a dose range of 0.48 to 3.95 mg/m^2 (1.4 to 8.9 mg actual administered). Based

on population PK analysis, no apparent relationship was observed between dose (0.2 to 10.6 mg) and apparent oral clearance, supporting dose-linearity within this dose range.

2.2.5.9 *How do the PK parameters change with time following chronic dosing?*

Following both IV and oral once weekly dosing, an approximately 2-fold accumulation for AUC was observed following Day 15 dose **(Tables 5 and 6)**. Trough concentrations increased through Cycle 1, suggesting that steady-state was not achieved by the time of last dose administration in a 28-day cycle.

2.2.5.10 *What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the major causes of variability?*

As mentioned in **Section 2.2.5.2**, all ixazomib clinical studies were conducted in patients. Following single-dose administration of 4 mg ixazomib (Study C16018), the inter-patient variability (%CV) was estimated to be 54% C_{MAX} and 41-44% for AUC. Following multiple-dose administration of ixazomib (Study C16004), the inter-patient variability was 61-70% for C_{MAX} and 49-53% for AUC after Day 1 administration and 26-61% for C_{MAX} and 53% for AUC after Day 15 administration. Following multiple-dose administration of ixazomib in combination with LenDex (Study C16005), the inter-patient variability was 34-52% for C_{MAX} and 17-54% for AUC after Day 1 administration and 39-82% for C_{MAX} and 10-14% for AUC after Day 15 administration.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

No formal studies have been conducted to assess the effect of covariates such as age, sex, body surface area (BSA), race, hepatic impairment (mild) or renal impairment (mild, moderate) on exposure and response to ixazomib. However, internal Pharmacometrics Review and sponsor's population PK (popPK) analyses both showed that age, sex, BSA, race, smoking status, mild hepatic impairment or mild/moderate renal impairment are not clinically significant covariates on ixazomib exposure.

A list of covariate values included in the popPK analyses is shown in **Table 7**.

Table 7. Summary of covariate values included in the popPK analyses

Covariate	Median (range) or categories (%)
Age (years)	65 (23, 91)
Serum albumin (g/L)	39 (12, 55)
Alanine aminotransferase (U/L)	18 (5, 127)
Aspartate aminotransferase (U/L)	22 (4, 127)
Total bilirubin (μM)	7 (1.71, 39.3)
Body surface area (m^2)	1.88 (1.23, 2.67)
Creatinine clearance (mL/min)	86.8 (25.8, 297)
Serum creatinine concentration (μM)	80 (35, 327)
Hematocrit (proportion of 1)	0.35 (0.15, 0.54)
Hemoglobin (g/L)	116 (46, 168)
Height (cm)	167 (131, 193)
Route of administration	PO/IV: 85.7/14.3
Len/dex Combination	Single agent/Len/dex Combination : 29.9/70.1
Dosing regimen	Twice weekly/Once weekly: 25.8/74.2
Race	White/Black/Asian/Other: 79.9/5.56/11.7/2.91
Sex	Female/Male: 42.4/57.6
Smoking status	Never/Current/Former/Unknown: 33.1/4.37/18.5/44
Body weight (kg)	75.5 (36.7, 151)

(Sponsor's Population PK Report MIL-PKPD-MLN9708-021, Table 11)

Relationship between Body Size and Exposure

The popPK analysis did not identify body weight (median: 76 kg, range: 37-151 kg) as a significant covariate influencing ixazomib PK. Body surface area (median: 1.9 m^2, range: 1.2-2.7 m^2) was included as the only covariate in the final model to explain 13% of the variability on the second peripheral compartment (V4), however it was not found to influence ixazomib central clearance or volume of distribution. This supports sponsor's fixed dosing approach.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups?

See Sections below.

2.3.2.1 *Elderly*

The popPK analysis did not identify age (mean: 63 years, range: 23-91 years) including elderly age ($n \geq 65 = 396, \geq 75 = 100, \geq 85 = 7$) as a significant covariate influencing ixazomib PK. No dose adjustment is needed based on patient age.

2.3.2.2 *Pediatric*

The sponsor has not conducted clinical studies of ixazomib in pediatric patients. Ixazomib was

granted orphan drug designation on 02/18/11for multiple myeloma. As orphan drugs are not required to comply with PREA requirements, the sponsor will likely receive a waiver.

2.3.2.3 *Gender*

The popPK analysis did not identify sex (n= 457 male (58%), 330 female (42%)) as a significant covariate influencing ixazomib PK. No dose adjustment is needed based on patient sex.

2.3.2.4 *Race/Ethnicity*

The popPK analysis did not identify race (n=627 White (80%), 47 Black (6%), 90 Asian (11%), 23, Other (3%)) as a significant covariate influencing ixazomib PK. Asian patients were however found to have higher mean AUC than White patients (35% higher based on sponsor's analysis, 18% based on FDA's analysis) but with overlapping AUCs. No dose adjustment is needed based on patient's race.

2.3.2.5 *Renal Impairment*

The sponsor proposed the following dosing recommendations in patients with renal impairment (RI), which are acceptable:

- **Mild or Moderate RI:** no dose adjustment, based on popPK analysis
- **Severe RI or End-Stage Renal Disease (ESRD) requiring dialysis:** reduce to 3 mg, based on RI clinical study

Mild or Moderate RI (popPK analysis)

Patients with mild or moderate RI (CrCL ≥ 30 mL/min) were included in all ixazomib clinical studies. Based on popPK analysis, mild or moderate RI did not affect ixazomib PK. No dose adjustment is needed in patients with mild or moderate RI. Refer to Pharmacometrics Review in **Section 3.2** for details.

Severe RI or ESRD (clinical study)

Study Design

Study C16015 evaluated the PK and safety of a single-dose ixazomib in patients with normal renal function and those with severe RI or ESRD requiring hemodialysis. In Part A, patients received a single-dose of 3.0 mg ixazomib capsule on Day 1 with PK sampling until Day 15. Those who tolerated Part A dose went on to Part B in which ixazomib was administered orally on Days 1, 8, 15 of a 28-day cycle at 4 mg, or 3 or 2.3 mg depending on Part A tolerability and dose modification guidelines. A total of 41 patients were enrolled with 38 PK-evaluable patients (n=18 normal renal function, n=14 severe RI, n=6 ESRD). Plasma protein binding was measured. In Part A, PK samples were collected at the following times: pre-dose then post-dose 0.5, 1, 1.5, 2, 3, 4, 8, 24, 29 (ESRD patients only), 30 (ESRD patients only), 48, 72, 96, 120, 144, 168, 240, 264, 336 h. In Part B, PK samples were collected at the following times: pre-dose on Days 1, 8, 15 of Cycle 1, and pre-dose on Day 1 of Cycles 2, 3, 4.

Results

The results showed that plasma protein binding does not change significantly by renal function, as

seen in **Table 8** below.

Table 8. Plasma protein binding for ixazomib by renal function

	Renal Function Group		
Parameter	**Normal Function**	**Severe RI**	**ESRD**
N	11	13	5
Fraction unbound (f_u, %)	1.32±0.760	1.20±0.682	1.28 ±0.553
Fraction bound (f_b, %)	98.7±0.760	98.8±0.675	98.7±0.567

Data shown as mean ± standard deviation
(Source: Sponsor's C16015 Clinical Study Report, Table 11-a)

Plots of observed ixazomib C_{MAX} and AUC by renal function are shown in **Figure 7**, statistical analysis of results is shown in **Table 9**, and summary of observed TEAEs in **Table 10**. The results showed that severe RI or ESRD increased ixazomib AUC by 36-42%. Pre- and post-dialyzer ixazomib PK concentrations during hemodialysis were similar, indicating that ixazomib is not dialyzable.

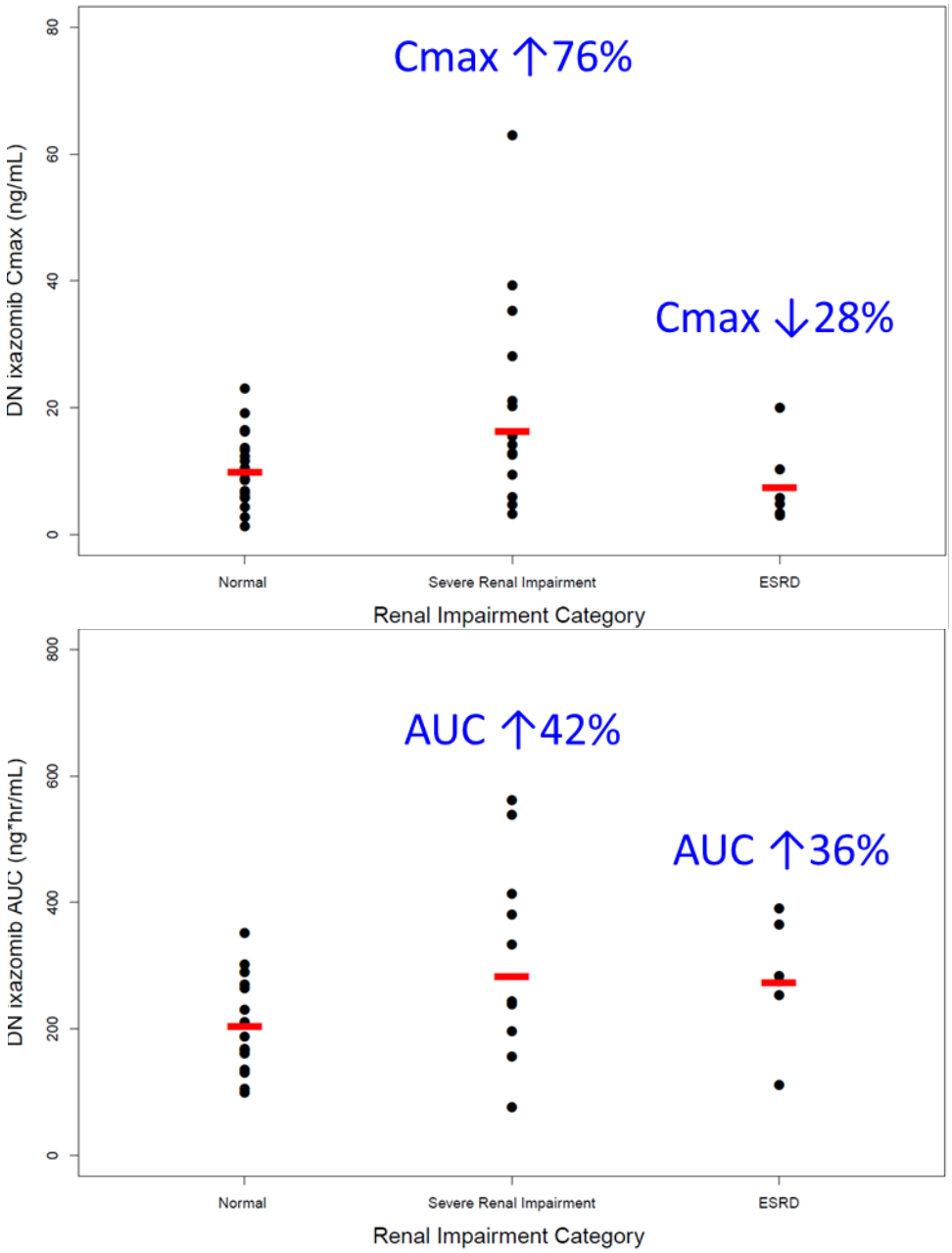


Figure 7. Plot comparison of ixazomib C_{MAX} (top) and AUC (bottom) by renal function (red bars denote the geometric mean).

Table 9. PK parameters and geometric least squares mean ratios for ixazomib C_{MAX} and AUC in renal impairment study

Parameter	Normal Renal Function	Severe RI	ESRD	Severe/Normal Ratio	ESRD/Normal Ratio
DN C_{MAX} (ng/ml/mg)	8.60 (56)	15.1 (80)	6.23 (82)	1.76	0.72
DN $AUC_{0\text{-LAST}}$ ((h·ng/ml/mg)	192 (38)	271 (51)	261 (35)	1.42	1.36
DN C_{MAX}	0.100 (66)	0.159 (86)	0.071 (57)	1.59	0.71

(ng/ml/mg, unbound)					
DN $AUC_{0\text{-LAST}}$ (h·ng/ml/mg, unbound)	2.21 (61)	3.08 (55)	2.97 (55)	1.39	1.34

where RI = renal impairment, ESRD = end-stage renal disease, DN = dose-normalized
values presented as geometric mean (CV%)

Table 10. Summary of treatment-emergent adverse events in renal impairment study

	Renal Function Group				
	Normal N=20 n (%)	Severe RI N=14 n (%)	ESRD N=7 n (%)	Severe RI/ ESRD N=21 n (%)	Total N=41 n (%)
Any TEAE	19 (95)	14 (100)	6 (86)	20 (95)	39 (95)
TEAE of ≥Grade 3 intensity	7 (35)	11 (79)	3 (43)	14 (67)	21 (51)
Study drug-related TEAE	16 (80)	12 (86)	4 (57)	16 (76)	32 (78)
Study drug-related TEAE of ≥Grade 3 intensity	6 (30)	7 (50)	1 (14)	8 (38)	14 (34)
SAE[a]	2 (10)	6 (43)	4 (57)	10 (48)	12 (29)
Drug-related SAE[a]	1 (5)	2 (14)	1 (14)	3 (14)	4 (10)
TEAE resulting in study drug discontinuation	2 (10)	4 (29)	0	4 (19)	6 (15)
TEAE resulting in dose reduction	5 (25)	5 (36)	0	5 (24)	10 (24)
TEAE resulting in dose modification	8 (40)	11 (79)	0	11 (52)	19 (46)
On-study deaths[b]	0	2 (14)	1 (14)	3 (14)	3 (7)

(Source: Sponsor's C16015 Clinical Study Report, Table 12-d)

The increased ixazomib AUC of up to 42% in patients with severe RI or ESRD and the exposure-safety findings (see **Section 3.1**) support the reduced ixazomib starting dose of 3 mg in patients with severe RI or ESRD requiring dialysis.

2.3.2.6 *Hepatic Impairment*

The sponsor proposed the following dosing recommendations in patients with hepatic impairment (HI), which are acceptable:

- **Mild HI:** no dose adjustment, based on popPK analysis
- **Moderate or Severe HI:** reduce to 3 mg, based on HI clinical study

Mild HI (popPK analysis)

Patients with mild HI (total bilirubin < 1.5 x ULN) were included in all ixazomib clinical studies. Based on a popPK analysis that included 83 subjects with mild HI, according to the NCI-ODWG criteria, mild HI was not found to be significant covariate on ixazomib PK. No dose adjustment is needed in patients with mild HI. Refer to Pharmacometrics Review in **Section 3.2** for details.

Moderate or Severe HI (clinical study)

Study Design

Study C16018 evaluated the PK and safety of a single-dose ixazomib in patients with normal hepatic function and those with moderate or severe HI (based on NCI definition of organ dysfunction). In Part A, patients received a single-dose dose of ixazomib capsule (4 mg for normal hepatic function, 2.3 mg for moderate HI, 1.5 mg for severe HI) with PK sampling until Day 15. Those who tolerated Part A dose went on to Part B in which ixazomib was administered orally on Days 1, 8, 15 of a 28-day cycle at the same dose in Part A or according to dose modification guidelines. A total of 48 patients were enrolled with 36 PK-evaluable patients (n=13 normal hepatic function, n=15 moderate HI, n=18 severe HI). Plasma protein binding was measured. In Part A, PK samples were collected at the following times: pre-dose, then post-dose 0.5, 1, 1.5, 2, 3, 4, 8, 24, 48, 72, 96, 120, 144, 168, 240, 264, 336 h. In Part B, PK samples were collected at the following times: pre-dose on Day 1 of Cycles 2, 3.

Results
The results showed that plasma protein binding does not change significantly by hepatic function, as seen in **Table 11** below.

Table 11. Plasma protein binding for ixazomib by hepatic function

	Hepatic Function Category		
Parameter	**Normal Function**	**Moderate Impairment**	**Severe Impairment**
N	12	15	19
Fraction unbound (%)	0.841 ± 0.346	0.926 ± 0.371	0.975 ± 0.462
Fraction bound (%)	99.2 ± 0.342	99.1 ± 0.372	99.0 ± 0.454

Data shown as mean ± standard deviation
(Source: Sponsor's C16015 Clinical Study Report, Table 11.a)

Plots of observed ixazomib C_{MAX} and AUC by hepatic function are shown in **Figure 8**, statistical analysis of results is shown in **Table 12**, and summary of observed TEAEs in **Table 13**. The results showed that moderate or severe HI increased ixazomib AUC by 13-27%.

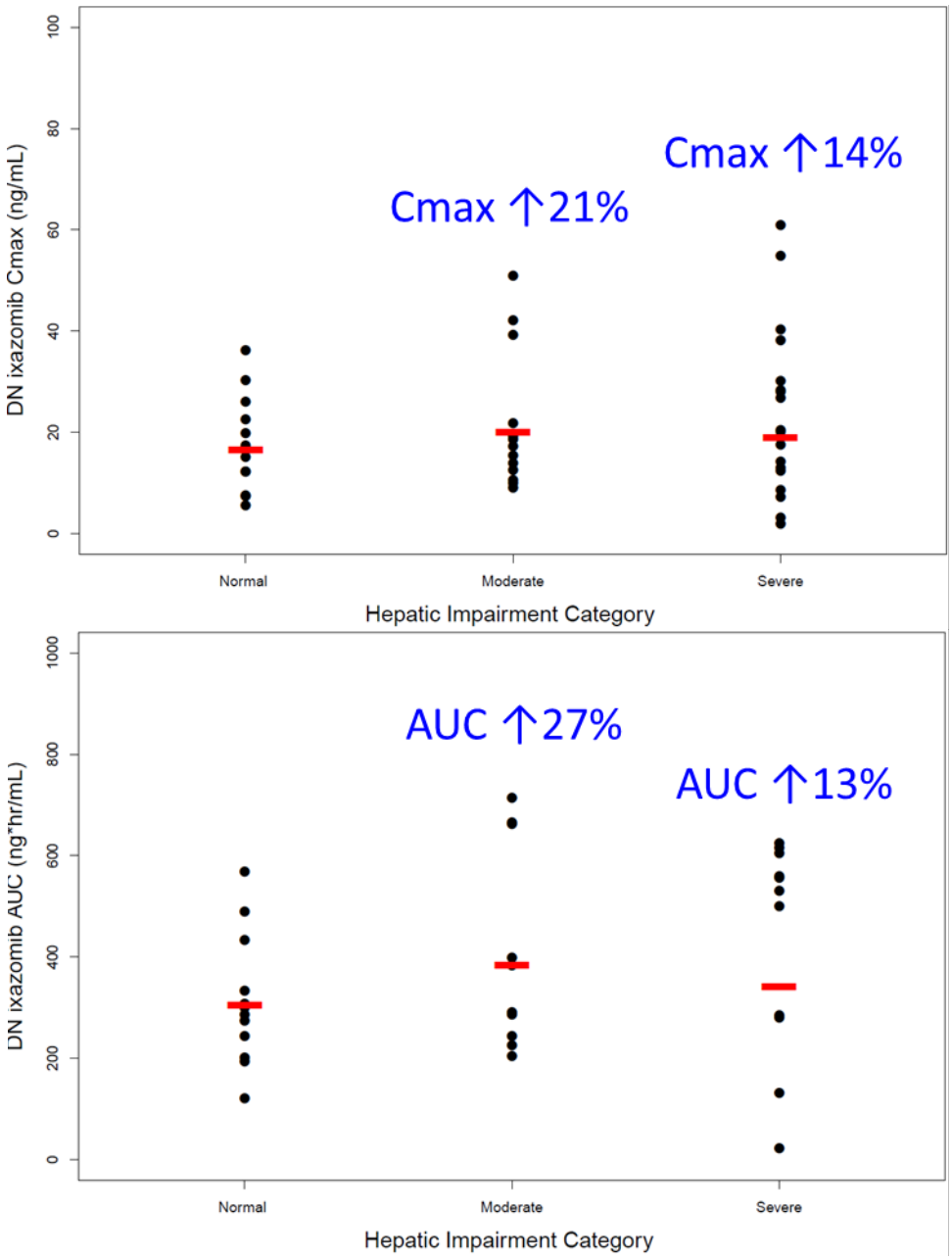


Figure 8. Plot comparison of ixazomib C_{MAX} (top) and AUC (bottom) by hepatic function (red bars denote the geometric mean).

Table 12. PK parameters and geometric least squares mean ratios for ixazomib C_{MAX} and AUC in hepatic impairment study

Parameter	Normal Hepatic Function	Moderate HI	Severe HI	Moderate/Normal Ratio	Severe/Normal Ratio
DN C_{MAX} (ng/ml/mg)	15.3 (54)	18.5 (63)	17.4 (70)	1.21	1.14
DN $AUC_{0\text{-LAST}}$ ((h·ng/ml/mg)	289 (41)	368 (49)	326 (49)	1.27	1.13

DN C_{MAX} (ng/ml/mg, unbound)	0.127 (47)	0.162 (80)	0.154 (84)	1.27	1.21
DN $AUC_{0\text{-}LAST}$ (h·ng/ml/mg, unbound)	2.41 (50)	3.19 (61)	2.96 (63)	1.32	1.23

where HI = hepatic impairment, DN = dose-normalized
values presented as geometric mean (CV%)

Table 13. Summary of treatment-emergent adverse events in renal impairment study

	Hepatic Function Group			
	Normal N=13 n (%)	Moderate Impairment N=15 n (%)	Severe Impairment N=20 n (%)	Total N=48 n (%)
Any adverse event	13 (100)	15 (100)	20 (100)	48 (100)
Grade 3 or higher adverse event	6 (46)	13 (87)	18 (90)	37 (77)
Drug-related adverse event	10 (77)	7 (47)	5 (25)	22 (46)
Grade 3 or higher drug-related adverse event	3 (23)	3 (20)	1 (5)	7 (15)
Serious adverse event	6 (46)	10 (67)	15 (75)	31 (65)
Drug-related serious adverse event	1 (8)	2 (13)	1 (5)	4 (8)
Adverse event resulting in study drug discontinuation	2 (15)	1 (7)	3 (15)	6 (13)
Adverse event resulting in dose reduction	0	0	0	0
Adverse event resulting in dose modification[a]	4 (31)	2 (13)	3 (15)	9 (19)
On-study deaths[b]	0	6 (40)	8 (40)	14 (29)

(Source: Sponsor's C16018 Clinical Study Report, Table 12.c)

The increased ixazomib AUC of up to 27 % in patients with moderate or severe HI and the exposure-safety findings (see **Section 3.1**) support the reduced ixazomib starting dose of 3 mg in patients with moderate or severe HI.

2.3.2.7 *What pregnancy and lactation use information is there in the application?*

There are no human data regarding the effect of ixazomib on pregnancy or the development of embryo or fetus, however embryo-fetal studies in animals showed that ixazomib has the potential to cause embryo-fetal lethality. (b) (4)

(b) (4)

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or dose-response and what is the impact of any differences in exposure on response?

See Sections below.

2.4.2 Drug-drug interactions

2.4.2.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

Yes, please see **Section 2.2.5.6** above and **Section 2.4.2.**2 below.

2.4.2.2 *Is the drug a substrate of CYP enzymes?*

Based on cytochrome P450 phenotyping in vitro studies (Report MLN9708-31259), it appears that non-CYP and, to a certain extent, CYP enzymes both contribute to ixazomib metabolism at clinical concentrations (0.1 and 0.5 µM) but at supra-therapeutic concentration (10 µM), it is primarily CYP-mediated with the following enzyme percent contributions: 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8), 2C9 (<1%).

2.4.2.3 *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

Inhibitor

In vitro studies did not identify ixazomib as a clinically relevant time-dependent or reversible inhibitor of CYP3A4, 1A2, 2B6, 2C8, 2C19, or 2D6 enzymes (IC_{50} > 30 µM, Ki > 15 µM).

Inducer

In vitro studies did not identify ixazomib as an inducer of CYP3A4, 1A2 or 2B6 enzymes (at concentrations up to 9.7 µM).

2.4.2.4 *Is the drug an inhibitor and/or an inducer of transporters?*

Inhibitor

In vitro studies did not identify ixazomib as a clinically relevant inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 or MATE2-K transporters.

Inducer

In vitro studies to evaluate ixazomib as an inducer of transporters were not conducted.

2.4.2.5 *Are there other metabolic/transporter pathways that may be important?*

P-gp Transporter: Based on Caco-2 cell studies, Ixazomib is a P-gp substrate as the net flux ratio was 2.9, and P-gp inhibitors (GF120918 and LY335979) reduced the efflux ratio of ixazomib by more than 2-fold **(Table 14)**. The binding affinity constant K_M was 239 µM and V_{MAX} was 575.1 pmol/h with a membrane permeation clearance V_{MAX}/K_M of 11 µL/h by passive diffusion and 2.4

µL/h by efflux transport. P-gp mediated transport of ixazomib contributed approximately 19% of its total transport. The studies seemed to indicate that ixazomib is not a high-affinity substrate of P-gp and that contribution of P-gp to overall ixazomib membrane permeation clearance is low.

Table 14. Efflux transport of ixazomib

Test Compounds	$P_{app,A\text{-}to\text{-}B} \times 10^{-6}$ [a] (cm/sec)	$P_{app,B\text{-}to\text{-}A} \times 10^{-6}$ (cm/sec)	Efflux Ratio (B:A)
MLN2238[b] (5 µM)	2.0 ± 0.5	5.8 ± 0.8	2.9
MLN2238[c] (50 µM)	2.2 ± 0.3	6.8 ± 0.8	3.1
MLN2238[b] + Ko143[d] (1 µM)	2.0 ± 0.4	3.9 ± 0.2	2.0
MLN2238[b] + GF120918[d] (2 µM)	3.3 ± 0.5	4.4 ± 0.1	1.3
MLN2238[b] + LY335979[d] (5 µM)	2.5 ± 0.9	3.6 ± 0.3	1.4
MLN2238[b] + indomethacin[d] (100 µM)	2.1 ± 0.4	3.4 ± 0.2	1.6

A-to-B = apical to basolateral; B-to-A = basolateral-to-apical; SEM = standard error of the mean

Note: Low permeability, $\leq 1 \times 10^{-6}$ cm/second; medium permeability, 1×10^{-6} cm/second to 10×10^{-6} cm/second; and high permeability, $\geq 10 \times 10^{-6}$ cm/second. An efflux ratio ($P_{app,B\text{-}to\text{-}A}/P_{app,A\text{-}to\text{-}B}$) >2 indicates that the test compound is an efflux pump substrate.

a Data expressed as mean ± SEM (n = 3).

b MLN2238 was tested at 5 µM.

c MLN2238 was tested at 50 µM.

d LY335979 is an inhibitor of P-gp, Ko143 is an inhibitor of BCRP, GF120918 is an inhibitor of P-gp and BCRP, and indomethacin is an inhibitor of MRP2.

(Source: Sponsor's RPT-01131 Amendment 2 Report, Table 1)

2.4.2.6 *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

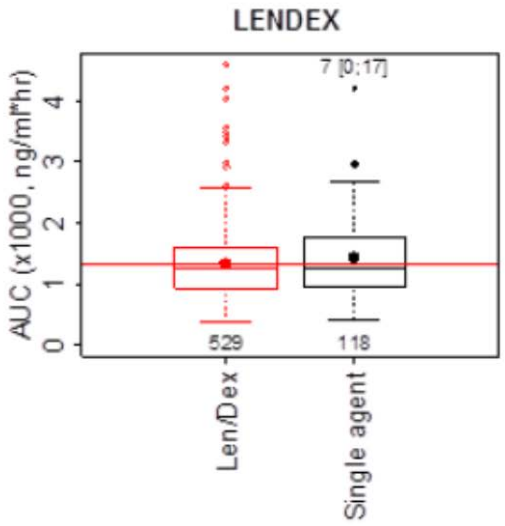
Yes, the labeling specifies administration of ixazomib in combination with lenalidomide and dexamethasone. The recommended starting doses for the combination agents are as follows:

- Lenalidomide: 25 mg daily on Days 1-21 of a 28-day treatment cycle
- Dexamethasone: 40 mg on Days 1, 8, 15 and 22 of a 28-day treatment cycle

No meaningful pharmacokinetic interaction is expected between ixazomib in combination with lenalidomide and dexamethasone, based on the following:

- Similar PK parameters for ixazomib when administered as a monotherapy (Studies C16003 and C16004) vs. when administered in combination with lenalidomide and dexamethasone (Studies C16005 and C16008). Population PK analyses also did not identify combination therapy with lenalidomide and dexamethasone as a significant covariate on ixazomib PK **(Figure 9)**.
- Ixazomib is not expected to affect the lenalidomide or dexamethasone PK for the following reasons: lenalidomide is predominantly renally cleared while dexamethasone is predominantly metabolized by CYP3A; ixazomib is not an inhibitor of CYP3A4 enzymes or

renal transporters.



Source: Population PK Report Figure 22.
Red and black dots indicate the mean exposure in the most prevalent category and in other categories. Numbers (brackets) in the top of plots show the percent change in $AUC_{0-\infty}$ (with 95%CI) in other categories relative to the most prevalent category, while numbers at the bottom show patients in each category.

Figure 9. Individual predicted AUC for ixazomib monotherapy or combination therapy with lenalidomide and dexamethasone.
(Source: Sponsor's Population PK Report MIL-PKPD-MLN9708-021, Figure 22)

2.4.2.7 *What other co-medications are likely to be administered to the target population?*

Concomitant medications used by ≥ 10% of patients in Phase 3 Study C16010 included drugs for anti-thrombotics, peptic ulcer and gastro-oesophageal reflux, analgesics and antipyretics, antivirals and opioids **(Table 15)**.

Table 15. Top concomitant medications used by ≥ 10% of patients in Phase 3 Study C16010

ATC Pharmacologic Subgroup WHO Generic Term	Placebo+LenDex N=362	Ixazomib+LenDex N=360	Total N=722
At least 1 concomitant medication	360 (100)	359 (100)	719 (100)
Antithrombotic agents	353 (98)	345 (96)	698 (97)
Acetylsalicylic acid	276 (77)	281 (78)	557 (77)
Enoxaparin	86 (24)	85 (24)	171 (24)
Nadroparin	40 (11)	25 (7)	65 (9)
Drugs for peptic ulcer and gastro-oesophageal reflux	259 (72)	268 (74)	527 (73)
Omeprazole	141 (39)	127 (35)	268 (37)
Pantoprazole	57 (16)	71 (20)	128 (18)
Esomeprazole	33 (9)	41 (11)	74 (10)
Other analgesics and antipyretics	239 (66)	221 (61)	460 (64)
Paracetamol	202 (56)	181 (50)	383 (53)
Direct acting antivirals	216 (60)	231 (64)	447 (62)
Aciclovir	148 (41)	157 (44)	305 (42)
Valaciclovir	65 (18)	77 (21)	142 (20)
Opioids	188 (52)	171 (48)	359 (50)
Tramadol	69 (19)	62 (17)	131 (18)
Oxycodone	57 (16)	51 (14)	108 (15)
Morphine	53 (15)	41 (11)	94 (13)
Fentanyl	42 (12)	31 (9)	73 (10)

(Source: Sponsor's C16010 Clinical Study Report, Table 10.i)

2.4.2.8 *Are there any in vivo drug-drug interaction (DDI) studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

Yes, see below.

DDI with Strong CYP3A4 Modulators

Preamble:

Study C16009 was a 5-arm study to evaluate the following:

- **ARM 1**: ketoconazole DDI (see below)
- **ARM 2**: relative bioavailability between Capsule A and Capsule B formulation (see Section 2.5.2)
- **ARM 3**: food effect (see Section 2.5.3)
- **ARM 4**: rifampin DDI (see below)
- **ARM 5**: clarithromycin DDI (see below)

The sponsor reported that based on statistical analyses of PK data from ARMS 2 and 3, which employed a 2-way cross-over with randomized sequence design, an "unexpected and unknown period effect" on ixazomib plasma exposures was observed—specifically, higher ixazomib exposures were observed in Period 2 vs. Period 1 (1.6-fold higher in ARM 2, 2.2-fold higher in

ARM 3). In ARMS 2 and 3, ixazomib was administered to patients on Day 1 and Day 15. Since ARM 1 utilized a fixed sequence design in which ixazomib was also administered to patients on Day1 and 15 (alone on Day 1 and with concomitant ketoconazole on Day 15), the sponsor determined that this study was confounded due to the observed period effect in Arms 2 and 3, which had the same ixazomib dosing interval as ARM 1. To overcome the period effect, the sponsor then modified ARM 4 design and added ARM 5 with only the experimental arm while referencing ARM 2/Period 1 as the control arm for ARM 4, and ARM1/Period 1 as the control arm for ARM 5. Overall study design is shown in **Figure 10**.

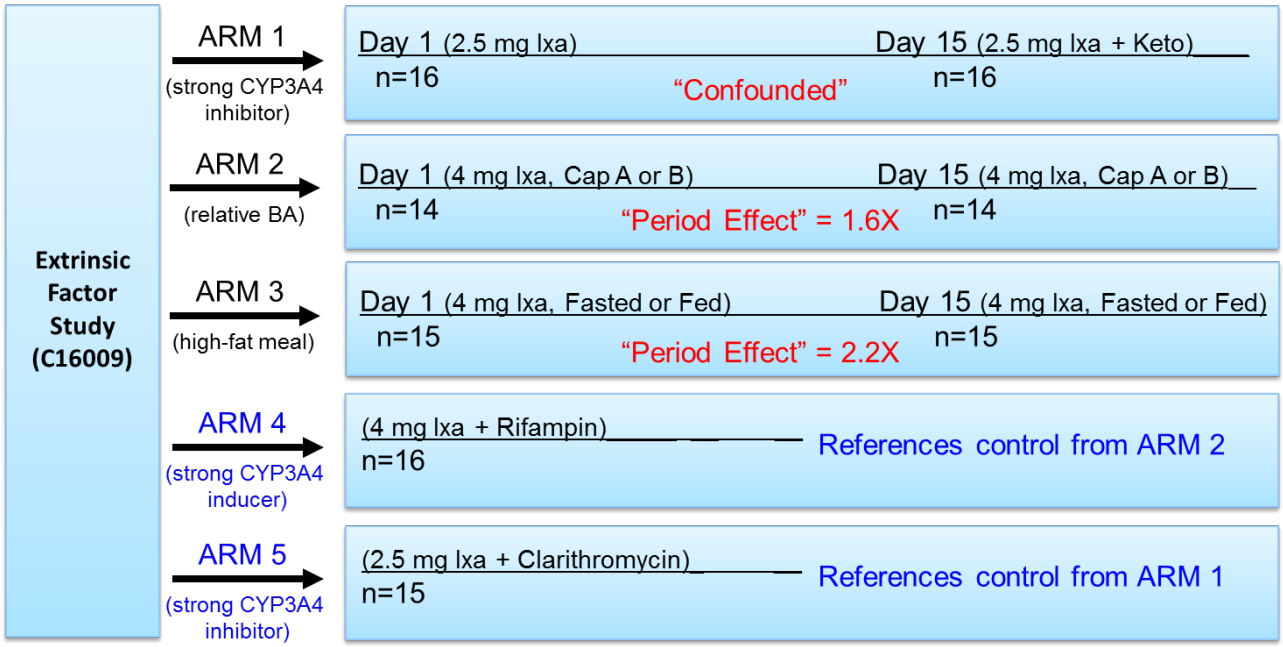


Figure 10. Study C16009 design.

It is worth noting that the unknown period effect is likely attributed to an inadequate washout time between dosing periods. Since ixazomib has a half-life of 5-10 h (based on non-compartmental and population PK analyses), a washout period of 14 d, as used in sponsor's original design, is insufficient for complete elimination of ixazomib. Reviewer's analysis of Period 2 pre-dose concentrations from ARMS 2 and 3 showed residual ixazomib concentrations from Period 1. Since ixazomib can only be administered in patients for whom cannot be withheld drug for a long washout period, the reviewer agrees with sponsor's updated designs for ARMS 4 and 5 to evaluate the DDI effect of concomitant strong CYP3A4 modulators on ixazomib PK. Details of the DDI studies (ARMS 1, 4, 5) are provided below.

DDI with Strong CYP3A Inhibitors

ARM 1: To evaluate the effect of ketoconazole (a strong CYP3A4 inhibitor) on single-dose ixazomib PK, the sponsor conducted an in vivo fixed sequence study in patients by administering ixazomib alone or in the presence of ketoconazole, as outlined below:

- **Period 1**: 2.5 mg ixazomib single dose was administered on Day 1 alone in patients. Ixazomib PK samples were collected at the following time points: pre-dose then post-dose on Days 1 (30 m, 1, 1.5, 2, 3, 4, 8 h), 2, 3, 4, 5, 6, 7, 8, 11, 12.
- **Period 2**: 2.5 mg ixazomib single dose was administered on Day 15 with concomitant ketoconazole in same patients from Period 1. 400 mg ketoconazole QD was administered on Days 12-25. Ixazomib PK samples were collected at the following time points: pre-dose then post-dose on Days 15 (30 m, 1, 1.5, 2, 3, 4, 8 h), 16, 17, 18, 19, 20, 21, 22, 25, 26.
- **Results**: a least-squares geometric mean ratio of 1.01 was observed for C_{MAX} and 2.08 for $AUC_{0\text{-}264h}$, as seen in **Table 16**.
- **Conclusion:** The results of this study are likely confounded (i.e., ixazomib exposure in presence of ketoconazole is over-estimated) by the period effect observed in ARMS 2 and 3 (discussed in the above **Preamble**). To resolve this issue, the sponsor added clarithromycin DDI study as ARM 5 with an updated design, discussed below.

Table 16. Effect of concomitant ketoconazole on ixazomib PK

Parameter	Ixazomib alone (Reference)	Ixazomib + Ketoconazole (Test)	LS Geometric Mean Ratio (90% CI) (Test / Reference)
N	16	16	
T_{max} (hr)	1.09 (0.47 - 2.07)	1.50 (0.50 - 4.17)	
C_{max} (ng/mL)	39.0 (48)	39.3 (61)	1.01 (0.78-1.30)
$AUC_{0\text{-}264}$ (ng•hr /mL)	552 (33)	1150 (46)	2.08 (1.91-2.27)

Source: C16009 Table 11.b.
Abbreviations: $AUC_{0\text{-}264}$=area under the plasma ixazomib concentration-time curve from time 0 to 264 hours postdose; CI=confidence interval; C_{max}=maximum observed plasma concentration; LS = least squares; T_{max}=time of first C_{max}.
Parameters are presented as geometric mean (%CV), except for T_{max} which is presented as median (range).
(Source: Sponsor's C16009 Clinical Study Report, Table 11.b)

ARM 5: To evaluate the effect of clarithromycin (a strong CYP3A4 inhibitor) on the single-dose PK of ixazomib, the sponsor conducted an in vivo single-period study in patients by administering ixazomib in the presence of clarithromycin. The PK data from ARM 1/Period 1 were used as a comparator **(see Figure 11)**. In ARM 5, patients were treated with 500 mg of clarithromycin twice daily on Days 1-16. On Day 6, 2.5 mg ixazomib was given in combination with clarithromycin and rich PK samples were collected until Day 17 post-dose. Ixazomib C_{MAX} and AUC did not show meaningful change when given in combination with clarithromycin **(Table 17)**. There is no significant DDI effect of concomitant clarithromycin on ixazomib PK.

Table 17. Effect of concomitant clarithromycin on ixazomib PK

Parameter	Ixazomib alone (Reference)	Ixazomib + Clarithromycin (Test)	LS Geometric Mean Ratio (90% CI) (Test / Reference)
N	16	15	-
T_{max} (hr)	1.09 (0.47-2.07)	1 (0.42-7.18)	-
C_{max} (ng/mL)	39.0 (48)	37.2 (50)	0.96 (0.67-1.36)
AUC_{0-264} (ng•hr /mL)	552 (33)	613 (54)	1.11 (0.86-1.43)

Source: C16009 Addendum Table 2.e.
Abbreviations: AUC_{0-264}=area under the plasma ixazomib concentration-time curve from time 0 to 264 hours postdose; CI=confidence interval; C_{max}=maximum observed plasma concentration; LS = least squares; T_{max}=time of first C_{max}.
Parameters are presented as geometric mean (%CV), except for T_{max} which is presented as median (range).
(Source: Sponsor's C16009 Clinical Study Report Addendum, Table 2.e)

Combined Ketoconazole and Clarithromycin DDI Analysis

Individual AUC and C_{MAX} observed in the ketoconazole and clarithromycin DDI studies are shown in **Figures 11 and 12**, respectively. Regarding the ketoconazole study, when considering a period effect of 1.6-2.2X on AUC, the net effect of ketoconazole on ixazomib PK becomes minimal to none. No clinically meaningful DDI effect was observed in the clarithromycin study. Therefore, when taken together, both the ketoconazole and clarithromycin study results support sponsor's recommendation of no dosing adjustment in patients who are on concomitant strong CYP3A4 inhibitors.

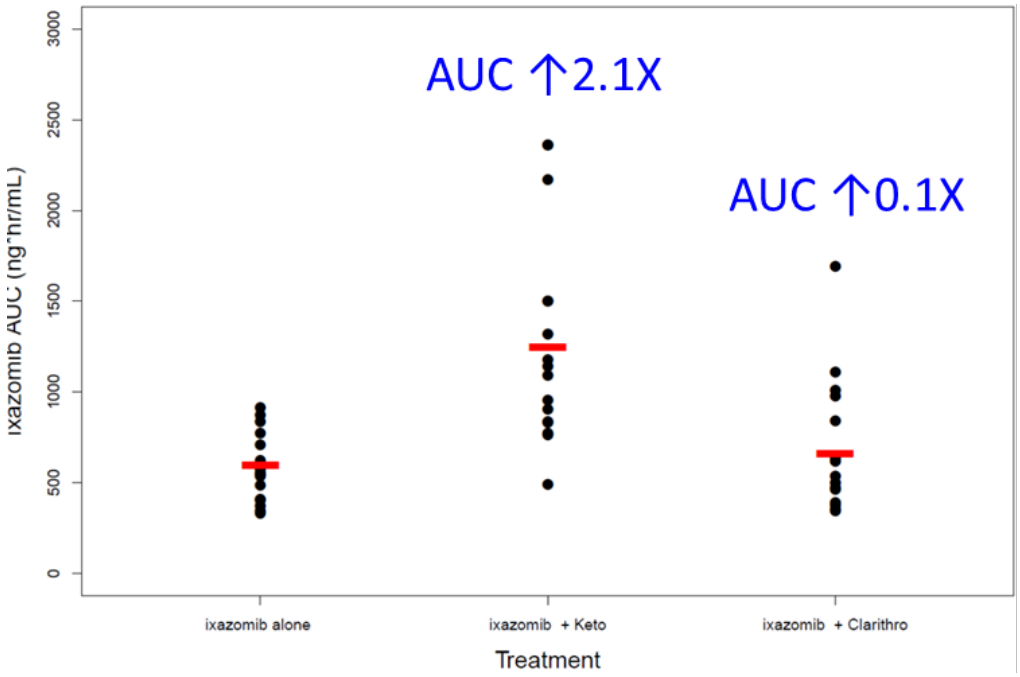


Figure 11. Individual AUC from the ketoconazole and clarithromycin DDI studies (red bars denote the geometric mean).

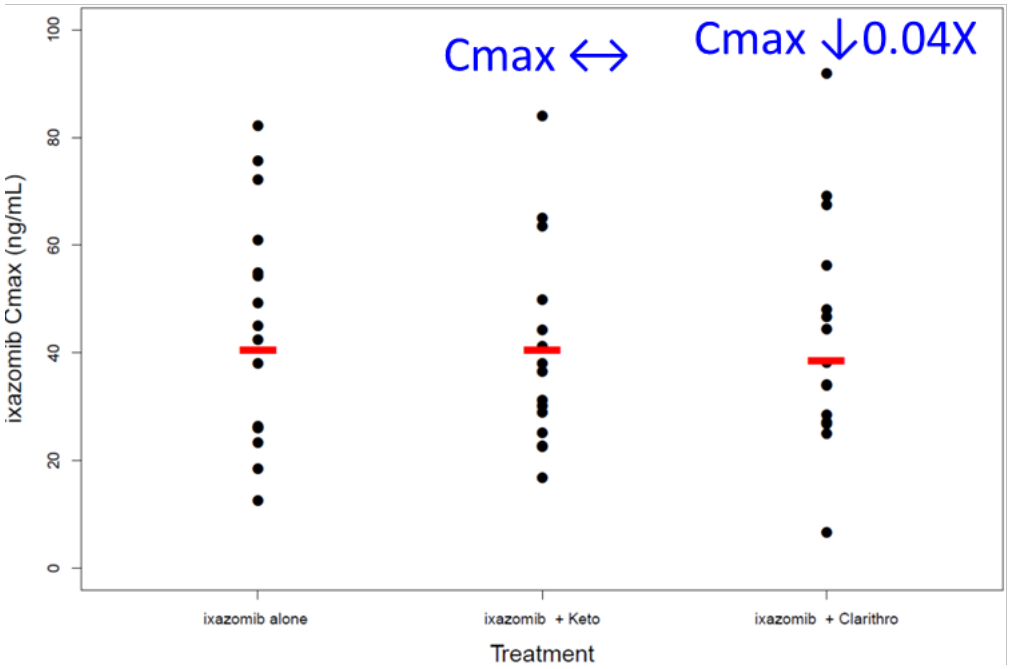


Figure 12. Individual C_{MAX} from the ketoconazole and clarithromycin DDI studies (red bars denote the geometric mean).

DDI with Strong CYP3A Inducer

To evaluate the effect of clarithromycin (a strong CYP3A4 inhibitor) on the single-dose PK of ixazomib, the sponsor conducted an in vivo single-period study in patients by administering ixazomib in the presence of clarithromycin. The PK data from ARM 1/Period 1 were used as a comparator (see **Figure 10**). In ARM 5, patients were treated with 500 mg of clarithromycin twice daily on Days 1-16. On Day 6, 2.5 mg ixazomib was given in combination with clarithromycin and rich PK samples were collected until Day 17 post-dose. Ixazomib C_{MAX} and AUC did not show meaningful change when given in combination with clarithromycin **(Table 17)**. There is no significant DDI effect of concomitant clarithromycin on ixazomib PK.

ARM 4: To evaluate the effect of rifampin (a strong CYP3A4 inducer) on single-dose ixazomib PK, the sponsor conducted an in vivo single-period study in patients by administering ixazomib in the presence of rifampin. The PK data from ARM 2/Period 1 were used as a comparator (see **Figure 10**). In ARM 4, patients were treated with 600 mg rifampin once daily on Days 1-14. On Day 8, 4 mg ixazomib was given in combination with rifampin and rich PK samples were collected until Day 15 post-dose. Concomitant administration with rifampin decreased Ixazomib C_{MAX} and AUC by approximately 54% and 74%, respectively **(Table 18)**. There is a significant DDI effect of concomitant rifampin on ixazomib PK.

Table 18. Effect of concomitant rifampin on ixazomib PK

Parameter [a]	Ixazomib alone (Reference)	Ixazomib + Rifampin (Test)	LS Geometric Mean Ratio (90% CI) (Test / Reference)
N	14	16	-
T_{max} (hr)	1.49 (0.5-7.5)	1.45 (0.5, 4.12)	-
C_{max} (ng/mL)	55.8 (57)	25.7 (50)	0.46 (0.29-0.73)
$AUC_{0\text{-last}}$ (ng•hr /mL)	907 (44)	232 (50)	0.26 (0.18-0.37)

Source: C16009 Table 11.e.
Abbreviations: $AUC_{0\text{-last}}$=area under the plasma ixazomib concentration-time curve from time 0 to the time of the last quantifiable concentration; CI=confidence interval; C_{max}=maximum observed plasma concentration; LS = least squares; T_{max}=time of first C_{max}.
a Parameters are presented as geometric mean (%CV), except for T_{max} which is presented as median (range).
(Source: Sponsor's C16009 Clinical Study Report, Table 11.e)

Rifampin DDI Analysis

Individual AUC and C_{MAX} observed in the rifampin DDI study are shown in **Figures 13 and 14**, respectively. Due to the significant exposure decrease of ixazomib in the presence of rifampin, the study results support sponsor's recommendation of avoid concomitant use of strong CYP3A4 inducers with ixazomib.

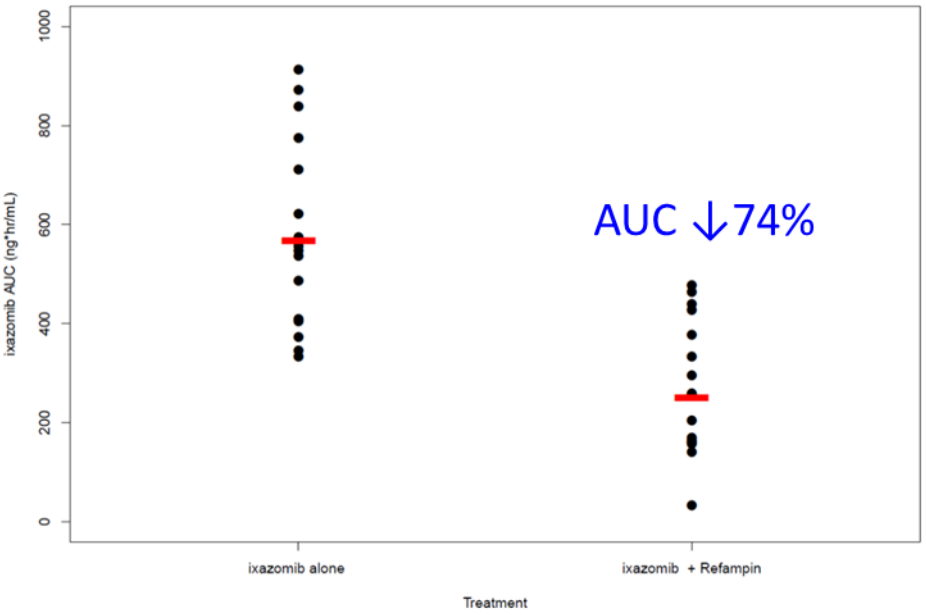


Figure 13. Individual AUC from the rifampin DDI study (red bars denote the geometric mean).

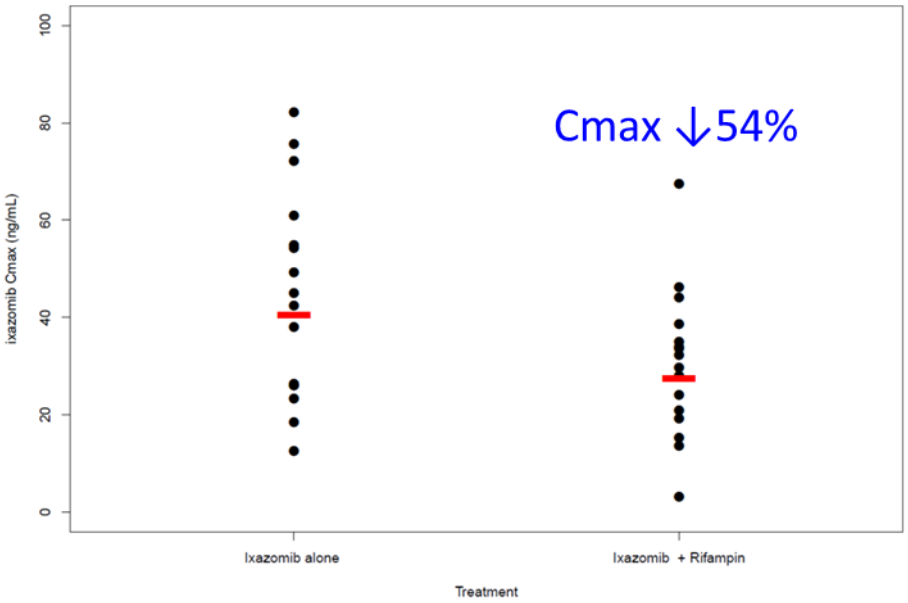


Figure 14. Individual C_{MAX} from the rifampin DDI study (red bars denote the geometric mean).

DDI with Strong CYP1A2 Modulators

No meaningful interaction is expected between ixazomib and strong CYP1A2 modulators, due to the following reasons:

Strong CYP1A2 Inhibitors

Clinical studies with concomitant strong CYP3A4 inhibitors ketoconazole (when considering the period effect) or clarithromycin did not influence the PK of ixazomib (see **Section above**). Given that CYP1A2 contributes less to ixazomib metabolism than CYP3A4 (42% by CYP3A4 vs. 26% by CYP1A2, sponsor's Report MLN9708-31259) and also considering ixazomib metabolism by non-CYP pathways, it is unlikely then that concomitant CYP1A2 inhibitors will have any significant or meaningful effect on ixazomib PK. These recommendations are also supported by a population PK analysis where the estimated effect size of strong CYP1A2 inhibitors on ixazomib exposure was small and statistically insignificant. Sponsor's recommendation of no dose adjustment in patients on concomitant strong CYP1A2 inhibitors is therefore acceptable.

CYP1A2 Inducers

Smoking is known to be a moderate CYP1A2 inducer. Based on population PK analyses of smokers in the Phase 3 Study C16010, smoking status (n=33 current smokers) was not found to be a significant covariate affecting ixazomib PK (decreased ixazomib AUC by 3.4%, see **Section 3.2**). It is therefore acceptable that no dose adjustment be recommended in patients on concomitant CYP1A2 inducers, including for patients who are smokers.

2.4.2.9*Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?*

No.

2.4.2.10 ***Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?***

Metabolite profiling is currently ongoing in the mass balance study (Study C16016).

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Ixazomib is classified as BCS Class III compound based on the following information (Report MLN9708-23928):

- High solubility—dose/solubility volume (b) (4) mL across physiological range
- Low permeability—apparent permeability at (b) (4)

2.5.2 What is the relative bioavailability of the (b) (4) formulation to the clinical trial formulation?

During ixazomib clinical development as an oral agent, 2 formulations were used: Capsule A and Capsule B. Capsule A formulation consisted of a (b) (4) drug substance and microcrystalline cellulose (MCC). Capsule B formulation consisted of drug substance, MCC, talc, and magnesium stearate. Capsule A was used in the 2 Phase 1 ixazomib monotherapy studies (Studies 16003 and 16004). All remaining clinical studies used Capsule B, including Phase 3 Study C16010, and it is the to-be-marketed formulation. To bridge their clinical studies, the sponsor evaluated the relative bioavailability between Capsule A and Capsule B in Study C16009, as outlined below:

ARM 2 (Study C16009):
To characterize the relative bioavailability of Capsule B in reference to Capsule A, the sponsor conducted an in vivo 2-sequence, 2-period cross-over study in which patients were randomized 1:1 to either capsule treatment sequence.

- **Design**: Patients were randomized according to sequence to receive 4 mg single dose ixazomib Capsule A or Capsule B on Day 1 followed by 4 mg single dose ixazomib of the alternate Capsule on Day 15 of a 28-day PK cycle. Ixazomib PK samples were collected at the following time points: pre-dose then post-dose on Days 1 (30 m, 1, 1.5, 2, 3, 4, 8 h), 2, 3, 4, 5, 8, 9, 10 and pre-dose then post-dose on Days 15 (30 m, 1, 1.5, 2, 3, 4, 8 h), 16, 17, 18, 19, 22, 23, 24.
- **Results**: ANOVA analysis showed a period effect for $AUC_{0\text{-}216h}$ indicating ~1.6-fold higher exposures in Period 2 vs. Period 1. This period effect was incorporated in the statistical analysis during the estimation of least squares geometric mean ratios and its 90%

CI, results presented in **Table 19**. The results showed that ixazomib exposure (C_{MAX} and AUC) are similar following administration of Capsule A or Capsule B formulation.

- **Conclusion**: Ixazomib PK following Capsule A or Capsule B administration are similar. Additionally, based on the PK similarity between formulations, Period 1 of this ARM may be used as the control PK arm (4 mg ixazomib alone) for the rifampin DDI study in ARM 4.

Table 19. Effect of capsule formulation on ixazomib PK

Parameter[a]	Capsule A (Reference)	Capsule B (Test)	Least Squares Geometric Mean Ratio (90% CI) (Test / Reference)
N	14	14	-
T_{max} (hr)	1.29 (0.52-3.0)	1.25 (0.50-7.5)	-
C_{max} (ng/mL)	61.9 (64)	71.9 (52)	1.16 (0.84-1.61)
AUC_{0-216} (hr*ng/mL)	1280 (62)	1330 (77)	1.04 (0.91-1.18)

Source: Table 14.2.1.3B and Table 14.2.1.4B.

Abbreviations: AUC_{0-216}=area under the plasma concentration-time curve from time 0 to 216 hours postdose; CI=confidence interval; C_{max}=maximum observed plasma concentration; T_{max}=time of first C_{max}.

a Values are geometric mean (%CV) for AUC_{0-216} and C_{max}. Median and range are reported for T_{max}.

(Source: Sponsor's C16009 Clinical Study Report, Table 11.c)

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

In all ixazomib clinical studies, ixazomib was administered in fasted state. To characterize the effect of food on single-dose ixazomib PK, the sponsor conducted an in vivo 2-sequence, 2-period cross-over study in which patients were randomized 1:1 to either food condition sequence, as outlined below:

ARM 3 (Study C16009):

- **Design**: Patients were randomized according to sequence to receive 4 mg single dose ixazomib with or without a standard high-fat breakfast on Day 1 followed by 4 mg single dose ixazomib of the alternate food condition on Day 15 of a 28-day PK cycle. The high-fat meal consisted of the following: 2 fried or scrambled eggs, 2 strips of bacon, 2 slices of toasted bread with butter, hash brown, whole milk totaling approximately 56 g fat, 55 g carbohydrates, 32 g protein, 844 calories. Ixazomib PK samples were collected at the following time points: pre-dose then post-dose on Days 1 (30 m, 1, 1.5, 2, 3, 4, 8 h), 2, 3, 4, 5, 8, 9, 10 and pre-dose then post-dose on Days 15 (30 m, 1, 1.5, 2, 3, 4, 8 h), 16, 17, 18, 19, 22, 23, 24.
- **Results**: ANOVA analysis showed a period effect for AUC_{0-216h} indicating ~2.2-fold higher exposures in Period 2 vs. Period 1. This period effect was incorporated in the statistical analysis during the estimation of least squares geometric mean ratios and its 90% CI, results presented in **Table 20**. The results showed a high-fat meal decreased ixazomib C_{MAX} by 69% and AUC by 28%.

- **Conclusion**: Based on the above decreased ixazomib exposure with food and in consideration of consistency with all prior ixazomib clinical studies, sponsor's proposal of ixazomib administration at least 1 h before or 2 h after food is acceptable.

Table 20. Effect of high-fat meal on ixazomib PK

Parameter[a]	Fasted (Reference)	Fed (Test)	Least Squares Geometric Mean Ratio (90% CI) (Test / Reference)
N	15	15	-
T_{max} (hr)	1.02 (0.48-4.0)	4.0 (1.93-8.03)	-
C_{max} (ng/mL)	77.0 (57)	22.8 (54)	0.31 (0.21-0.45)
AUC_{0-216} (hr*ng/mL)	1470 (50)	999 (79)	0.72 (0.58-0.89)

Source: Table 14.2.1.3C and Table 14.2.1.4C.

Abbreviations: AUC_{0-216}=area under the plasma concentration-time curve from time 0 to 216 hours postdose; CI=confidence interval; C_{max}=maximum observed plasma concentration; PK=pharmacokinetic; T_{max}=time of first C_{max}

a Values are geometric mean (%CV) for AUC_{0-216} and C_{max}. Median and range are reported for T_{max}.

(Source: Sponsor's C16009 Clinical Study Report, Table 11.d)

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

Refer to Biopharmaceutics review.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

Ixazomib capsules will be provided in the following dosage strengths: 4.0, 3.0, 2.3 mg. Refer to Biopharmaceutics review.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?

Following administration of ixazomib citrate, the active pharmacological moiety is ixazomib. Ixazomib plasma concentrations were measured and analyzed using validated LC-MS/MS methods.

2.6.2 Which metabolites have been selected for analysis and why?

Ixazomib metabolites are not known to have pharmacological activity and were not measured in clinical studies.

2.6.3 For all moieties measured is free, bound or total measured?

Given that ixazomib is highly bound (99%) to human plasma proteins, total plasma concentrations were measured.

2.6.4 What bioanalytical methods are used to assess concentrations?

Ixazomib concentrations in human plasma were measured using validated LC-MS/MS methods. During ixazomib clinical development, 4 methods were developed to analyze ixazomib plasma concentrations as follows (b) (4) methods **(Table 21)**.

Table 21. PK assays used in ixazomib clinical studies

Clinical Study	Matrix	Analyte	Plasma Ixazomib Assay Method	Report Number
C16001	Plasma	Ixazomib	(b) (4)	TNJR08-309
C16002	Plasma/urine	Ixazomib	gelled	TNJR09-085
C16003	Plasma	Ixazomib	gelled	TNJR09-125
C16004	Plasma	Ixazomib	gelled	TNJR09-190
C16005	Plasma	Ixazomib	gelled	TNJR10-220
C16007	Plasma/whole blood	Ixazomib	gelled	TNJR10-251
C16008	Plasma	Ixazomib	Gelled, urea (a)	TNJR11-123
C16009	Plasma	Ixazomib	Gelled, urea (a)	TNJR11-144 and TNJR11-144 Addendum 1
C16010	Plasma	Ixazomib	Gelled, urea (a)	TNJR11-254
C16013	Plasma	Ixazomib	Gelled, urea (a)	TNJR12-032
C16015	Plasma	Ixazomib	Gelled, urea (a)	TNJR12-179
C16016	Plasma/urine	Ixazomib	Gelled, urea (a)	TNJR13-025
	Plasma/urine/whole blood/feces	^{14}C-ixazomib/total radioactivity	N/A	P 1238
	Plasma	Ixazomib/ixazomib enantiomer	Chiral assay	96N-1425
C16018	Plasma	Ixazomib	Gelled, urea (a)	TNJR13-078
TB-MC010034	Plasma	Ixazomib	Gelled, urea (a)	TNJR11-256

(a) The urea method was used for highly-gelled samples only.

(Source: Sponsor's 2.7.1 Summary of Biopharm Studies, Table 1.e)

2.6.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies?*

The range of standard curve for total ixazomib concentrations is 0.5 to 500 ng/mL. The standard curve range is adequate to determine ixazomib plasma concentrations in the clinical studies.

2.6.4.2 *What are the lower and upper limits of quantification?*

See **Section 2.6.4.1** above.

2.6.4.3 *What are the accuracy, precision and selectivity at these limits?*

Validated ixazomib PK assay accuracy and precision values are provided in **Table 22**.

Table 22. Validated ixazomib PK accuracy and precision values

Ixazomib PK Assay	Sponsor Report	Accuracy (% Bias)		Precision (% CV)	
		Intra-run	Inter-run	Intra-run	Inter-run
(b) (4) method: in human plasma	TNJR08-260	-5.2 to 12	-0.4 to 2.5	0.8 to 8.6	3.0 to 7.8
(b) (4) method: in human plasma	TNJR08-260 Addendum 1	-9.8 to -3.5	--	2.2 to 8.8	--
Gelled method: in human plasma	TNJR08-260 Addendum 2	-2.0 to -1.3	--	4.9 to 6.9	--
Urea method: in human plasma	TNJR08-260 Addendum 4	-3.5 to 12.4	-2.3 to 9.8	1.8 to 8.5	4.0 to 7.7
In human whole blood	TNJR10-143	-6.0 to 1.0	-4.5 to 0.0	1.0 to 8.8	2.1 to 6.4
In human urine	TNJR08-261	-5.8 to 5.3	-4.3 to 2.7	1.3 to 12	2.4 to 11

In regards to method selectivity, no interference was found at the retention times of interest using blank human plasma from 6 lots.

3 PHARMACOMETRICS APPENDICES

3.1 EXPOSURE-RESPONSE ANALYSES REVIEW

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRICS REVIEW:

EXPOSURE-RESPONSE ANALYSES FOR EFFICAY AND SAFETY

NDA/SDN	NDA 208462
Generic Name	Ixazomib
Receipt Date	1st Interim: July 10, 2015; 2nd Interim: October 9, 2015
Proposed Indication	Treatment of patients with multiple myeloma who have received at least one prior therapy
Dosage Form (Strengths)	Capsules (4.0, 3.0, 2.3 mg)
Route of Administration	Oral
Dosing Regimen and Strength	4 mg on Days 1, 8 and 15 of a 28-day cycle
Applicant	Millennium Pharmaceuticals, Inc.
OND Division	Division of Hematology Products
OCP Divisions	Division of Clinical Pharmacology V Division of Pharmacometrics
Pharmacometrics Reviewer	Jee Eun Lee, Ph.D.
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.

Table of Contents

1 SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions:

1.1 Is there evidence of exposure-response relationship for efficacy?

No. Within the exposure range observed in the Phase 3 trial, there appear to be no relationships between ixazomib exposure and efficacy endpoints including progression-free survival **(Figures 20 and 21)** and complete response. The studied start dose of 4 mg is one dose level lower than the MTD (5.5 mg corresponding to 2.97 mg/m^2 for a typical patient) and data do not indicate that increasing ixazomib exposure would offer any additional benefit. In addition, the baseline risk factors among the four exposure quartiles seem to be reasonably balanced and there were no relationships between baseline risk factors and exposures **(Figure 22)**.

1.2 Are the proposed dose modification schemes to manage adverse events reasonable?

Yes, but additional scheme is needed for gastrointestinal toxicities. Generally rates of incidences tend to increase with increasing ixazomib exposure for most of adverse events including thrombocytopenia, anemia, rash, peripheral neuropathy, diarrhea, nausea, vomiting. For the exposure-response analysis of safety, time averaged daily AUC prior to the adverse event was utilized as the exposure variable. Among those AEs, thrombocytopenia, rash and diarrhea show significant relationships with ixazomib exposure. The applicant proposes dose modification based on safety endpoints: thrombocytopenia, rash, peripheral neuropathy and gastrointestinal toxicities.

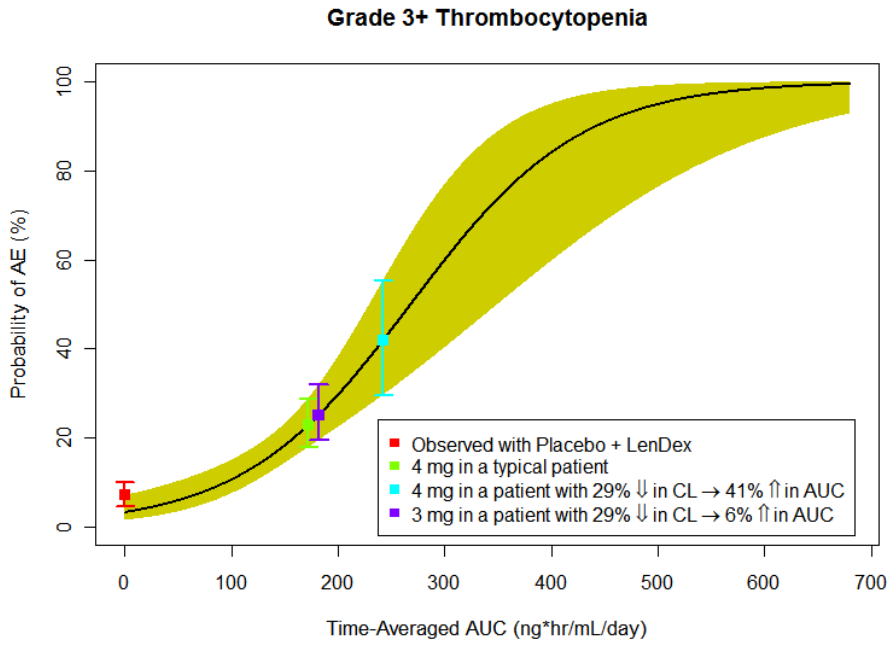


Figure 15. Probability of greater than Grade 3 thrombocytopenia vs. average daily AUC of ixazomib. The olive color shaded region represents the 95% confidence interval (CI). The observed rate (95% CI) in placebo+LenDex arm is in red, predicted adverse event rate (95% CI) for a typical patient with 4 mg dose in green, predicted adverse event rate (95% CI) for a patient with reduced clearance by 29% (patient with severe renal impairment) with 4 mg dose in light blue, and predicted adverse event rate (95% CI) for a patient with reduced clearance by 29% with 3 mg dose in purple.

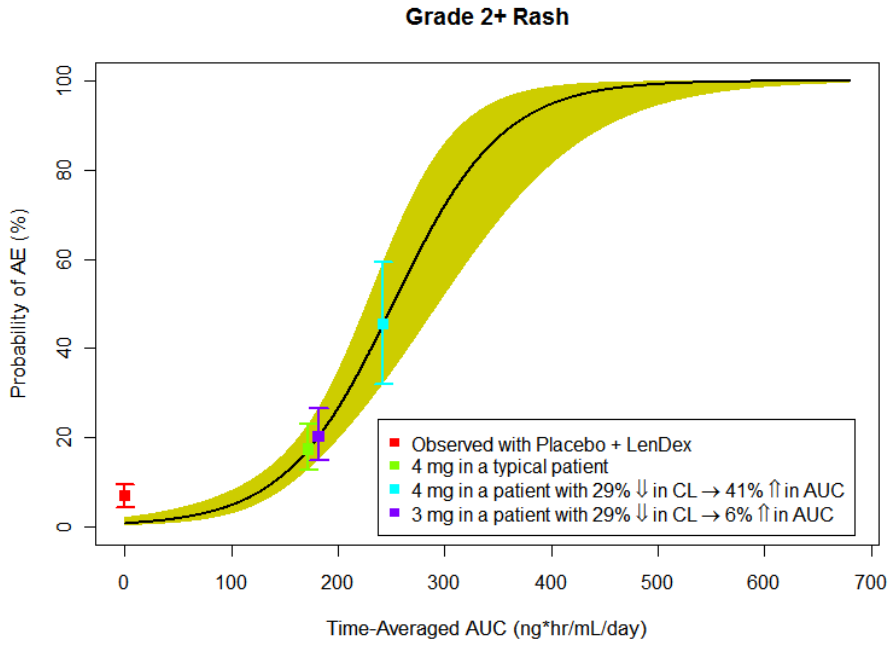


Figure 16. Probability of greater than Grade 2 rash vs. average daily AUC of ixazomib. The olive color shaded region represents the 95% confidence interval (CI). The observed rate (95% CI) in placebo+LenDex arm is in red, predicted adverse event rate (95% CI) for a typical patient with 4 mg dose in green, predicted adverse event rate (95% CI) for a patient with reduced clearance by 29% (patient with severe renal impairment) with 4 mg dose in light blue, and predicted adverse event rate (95% CI) for a patient with reduced clearance by 29% with 3 mg dose in purple.

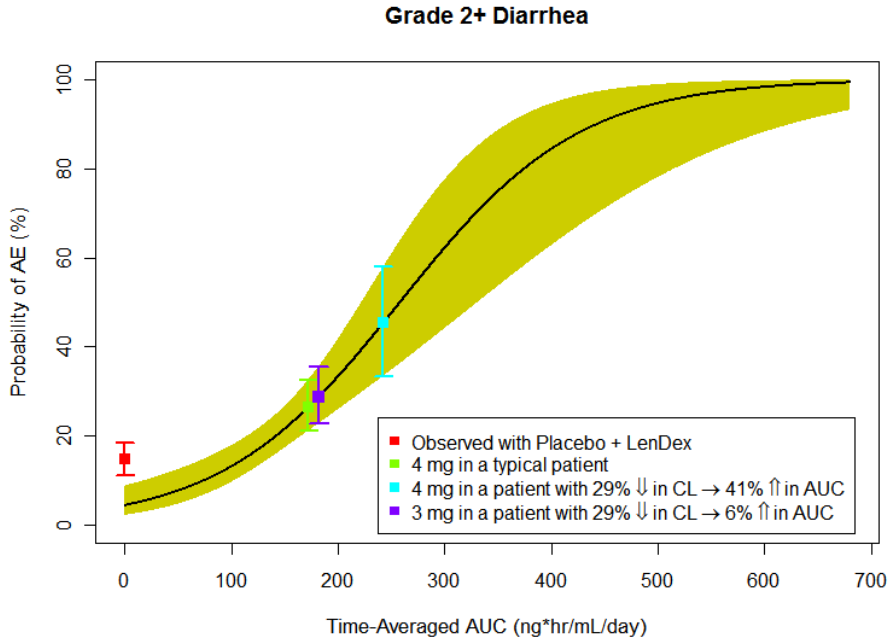


Figure 17. Probability of greater than Grade 2 diarrhea vs. average daily AUC of ixazomib. The olive color shaded region represents the 95% confidence interval (CI). The observed rate (95% CI) in placebo+LenDex arm is in red, predicted adverse event rate (95% CI) for a typical patient with 4 mg dose in green, predicted adverse event rate (95% CI) for a patient with reduced clearance by 29% (patient with severe renal impairment) with 4 mg dose in light blue, and predicted adverse event rate (95% CI) for a patient with reduced clearance by 29% with 3 mg dose in purple.

As shown in **Figure 15, Figure 16 and Figure 17**, the probability of having an event of thrombocytopenia, rash or diarrhea increases with increasing time-averaged daily AUC (average daily dose up to the date of event/individual clearance predicted by population PK model). The applicant proposes to modify dose based on thrombocytopenia, rash or peripheral neuropathy and the step size for the reduction is summarized below:

Recommended starting dose*	First reduction to	Second reduction to	Discontinue
4 mg	3 mg	2.3 mg	

If platelet count drops below 30,000/mm^3, both ixazomib and lenalidomide are to be withheld until recovery. Upon recovery, treatment is to start with reduced dose of lenalidomide dose and the same dose of ixazomib. If platelet count falls to <30,000/mm^3 again, then ixazomib dose is reduced to next lower dose. The same scenario is proposed for greater than Grade 2 rash and for greater than Grade 2 neuropathy. However, the proposed labeling indicates a need of dose adjustment for severe gastrotoxicities including diarrhea in "Warnings and Precautions" section (b) (4)

The exposure-response relationships for thrombocytopenia and rash support the proposed dose modification schemes based on these safety endpoints. Furthermore, dose modification based on gastrointestinal toxicities such as diarrhea should be included as well as these safety endpoints.

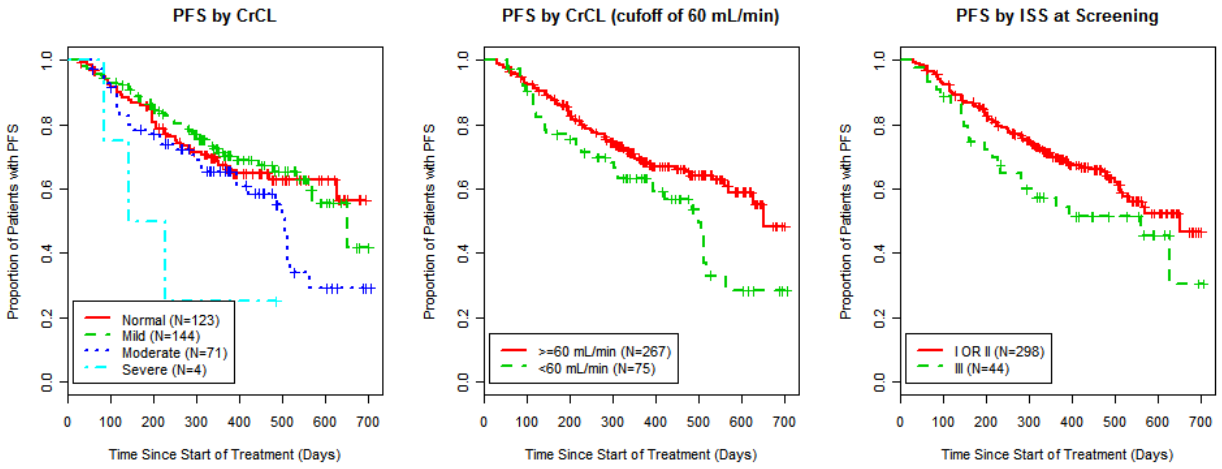
1.3 Are the proposed dose reductions for the starting dose in patients with moderate/severe hepatic impairment, severe renal impairment, or ESRD requiring hemodialysis reasonable?

Yes. Based on the exposure-response relationships for safety endpoints including thrombocytopenia, rash, and anemia, the higher of adverse events is predicted with higher exposure of ixazomib. Therefore, reduced dose of ixazomib to 3 mg for patients with increased exposures appears to be reasonable.

As shown in **Figure 15**, the predicted event rate of thrombocytopenia for a patient with typical clearance following 4 mg dose of ixazomib was estimated to be ~23%. If the clearance is reduced in a patient due to severe hepatic impariment or severe renal impairment, the probability of having thrombocytopenia increases. From Study C16018, the applicant found that AUCs in patients with moderate hepatic impairment and severe impairment increased by 32% and 23%, respectivly. From Study C16015, AUC in patients with severe renal impairment was found to be 39% higher compared to patients with normal renal function. If a reduced dose of 3 mg is given to patients with reduced clearance of drug by ~29%, the predicted probability of having thrombocytopenia is reduced to the value which is close to the typical patient with 4 mg dose of ixazomib **(Figure 15)**. Similar trends were observed with other safety endpoints such as a rash or diarrhea **(Figure 16, Figure 17)** Therefore, the applicant's proposed starting dose of 3 mg for patients with moderate/severe hepatic impairment, severe rennal impairment or ESRD requiring hemodialysis appear to be reasonable.

1.4 Is the difference in PFS between patients with CrCL <60 mL/min and those with CrCL ≥60 mL/min due to the difference in the drug disposition or drug action in these groups of patients?

It is unlikely. There was no significant difference in ixazomib PK between patients with different renal function (see **Section 3**. Reviewer's analysis) which is consistent with negligible excretion of ixazomib in urine as unchanged drug (~3%). The apparent effect of creatinine clearance on PFS appears to be due the difference in the baseline disease condition. Furthermore, deterioration of renal function has been reported to be associated with disease progression of multiple myeloma.



(a) (b) (c)

Figure 18. Kaplan-Meier survival curves by CrCL and ISS. The middle panel (b) shows PFS for patients with cutoff of CrCL 60 mL/min. Analysis was based on the 2nd interim PFS data submitted on Oct 9, 2015.

As shown in **Figure 18 (a)**, the difference in PFS by CrCL was driven by 4 patients with severe renal impairment. Generally, patients with severe renal impairment tend to be older and sicker; the reviewer conducted further analysis with ISS (International Staging System) which is an important prognostic metrics for multiple myeloma. As shown in **Figure 18 (c)**, the difference in PFS between patients with ISS I or II and those with ISS III is notable. Due to the difference in number of patients for those categories (CrCL ≥60 mL/min vs. <60 mL/min and ISS I or II vs. ISS III), the survival curves are not exactly aligned.

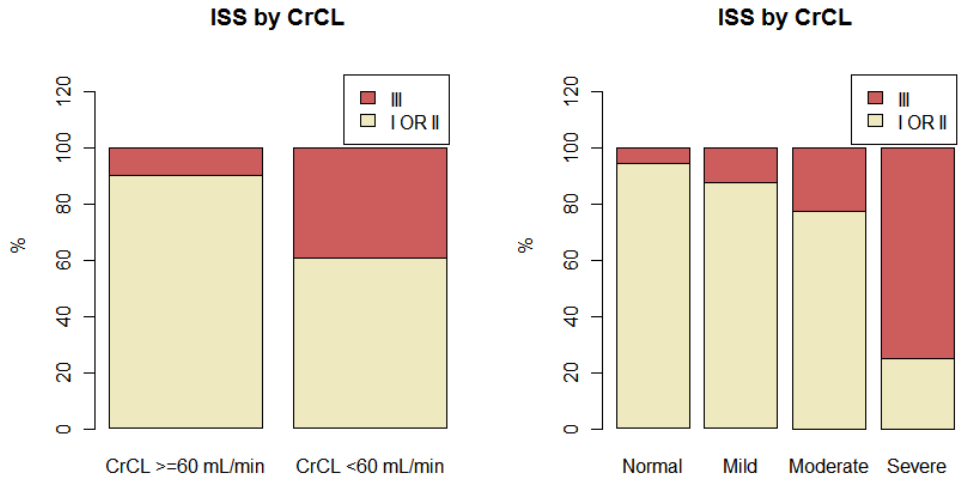


Figure 19. Distribution of patients by ISS in each category of CrCL.

As shown in **Figure 19**, higher portion of patients with ISS III (sicker patients) are included in the category of patients with poor baseline renal function. Therefore, the apparent effect of CrCL on PFS is likely due to the effect of baseline disease condition of PFS.

2 LABELING RECOMMENDATIONS

Detailed labeling revisions are summarized as below. The ~~strikethrough in red~~ text indicates recommended deletion by the reviewer. The texts in blue are recommended labeling changes by the reviewer.

Proposed labeling by the applicant	Labeling recommendations
DOSAGE AND ADMINISTRATION	Adjust dose based on thrombocytopenia, rash, or gastrointestinal toxicities such as diarrhea, nausea and/or vomiting (2.2).
2.2 Dose Modification Guidelines	*Update the guideline with additional rows for gastrointestinal toxicities*

3 APPLICANT'S ANALYSIS

3.1 Exposure metrics

The exposure metric for ixazomib in the E-R analyses was time-averaged systemic exposure (AUC/day), which was derived from individual predicted value of apparent clearance (CL/F) using population PK model and total dose given prior to the adverse event of interest.

$$Total\ AUC = \frac{Total\ Dose}{Oral\ Clearance}$$

$$Time\text{-}Averaged\ Exposure\ (or\ Exposure) = \frac{Total\ AUC}{Total\ Time\ to\ Event}$$

3.2 Exposure-response for efficacy

The exposure-PFS relationship was investigated by a proportional hazards model. The results from the analyses indicated ixazomib exposure, as a continuous variable, was not a significant predictor of PFS with a p-value of 0.2569 and a hazard ratio (95% CI) of 1.002 (0.998, 1.006). Therefore, no covariate analyses were performed to evaluate the potential effects of baseline risk factors on the ixazomib exposure-PFS. Analysis with ixazomib exposure quartile was also performed. Kaplan-Meier curve for PFS was generated (now shown) and **Table 23** summarizes the PFS by exposure quartile of ixazomib and **Table 24** summarizes clinical responses by exposure quartile of ixazomib. As shown in **Table 23** and **Table 24**, there were no clear relationship between ixazomib exposure and efficacy.

Table 23.PFS by Ixazomib Exposure Quartile Compared to Placebo Regimen

Exposure Group	N	Events[a] N (%)	Range of exposure (ng•hr/mL/day)	Median PFS Month (95%CI)	Hazard Ratio[b] (95% CI)
Ixazomib 1st Quartile	86	32 (37)	33.5-84.2	20.6 (12.9, NE)	0.675 (0.461, 0.989)
Ixazomib 2nd Quartile	85	29 (34)	84.8-117	21.4 (16.6, NE)	0.646 (0.434, 0.961)
Ixazomib 3rd Quartile	86	30 (35)	117-148	16.8 (15.4, NE)	0.748 (0.506, 1.105)
Ixazomib 4th Quartile	85	31 (36)	148-276	18.4 (17.0, NE)	0.794 (0.540, 1.167)
Placebo+LenDex	362	157 (43)		14.7 (12.9, 17.6)	

(Source: Ixazomib exposure-response report, Table 4.b., page 19)

Table 24. Summary of Best Clinical Responses for CR, ≥VGPR and ≥PR in the 4 Ixazomib Exposure Quartiles as Compared to the Placebo Regimen

	Placebo+ LenDex N=343	Ixazomib Exposure Quartile (ng•hr/mL/day)				
		1st Quartile N=85	2nd Quartile N=84	3rd Quartile N=85	4th Quartile N=84	Total N=338
CR (%)	23 (7)	4 (5)	8 (10)	16 (19)	14 (17)	42 (12)
Median AUC (range)		70.7 (36.0-85.5)	104 (86.2-119)	134 (119-152)	180 (153-344)	119 (36.0-344)
≥VGPR (%)	135 (39)	32 (38)	45 (54)	49 (58)	45 (54)	171 (51)
Median AUC (range)		72.1 (36.0-87.8)	106 (88.7-120)	134 (121-155)	180 (155-344)	121 (36.0-344)
≥PR (%)	253 (74)	71 (84)	74 (88)	65 (76)	69 (82)	279 (83)
Median AUC (range)		73.5 (38.4-87.8)	105 (89.9-120)	133 (121-156)	180 (156-344)	121 (38.4-344)

(Source: Ixazomib exposure-response report, Table 4.c., page 19)

3.3 Exposure-response for safety

Exposure-response analyses for safety endpoints were performed for various AEs, and covariate analysis performed to evaluate the potential effects of baseline risk factors on the ixazomib exposure-safety. The covariates included in the analyses were ECOG, ISS, cytogenetic risk, prior immunomodulatory drug therapy, prior lines of therapy (Prior therapy in the reviewer's analysis), prior proteasome-inhibitor therapy, creatinine clearance, and demographics.

Table 25 summarizes the event rate of hematological AEs by ixazomib exposure quartiles and **Table 26** summarizes the estimated Odds Ratio for those events. As shown in these tables, anemia and thrombocytopenia showed significant relationships with ixazomib exposure.

Table 25. Summary of Hematological AEs (≥Grade 3) by Ixazomib Exposure Quartiles as Compared to the Placebo Regimen

	Placebo+ LenDex N=360	Ixazomib Exposure Quartile (ng•hr/mL/day)				
		1st Quartile N=87	2nd Quartile N=87	3rd Quartile N=87	4th Quartile N=86	Total N=347
Anemia (%)	45 (13)	7 (8)	5 (6)	7 (8)	12 (14)	31 (9)
Median AUC		72.1	105	134	186	120
(Range)		(34.9-86.2)	(87.0-120)	(122-155)	(156-641)	(34.9-641)
Neutropenia (%)	71 (20)	16 (18)	18 (21)	19 (22)	16 (19)	69 (20)
Median AUC		72.1	109	138	186	123
(Range)		(34.9-87.5)	(87.7-123)	(123-157)	(157-357)	(34.9-357)
Thrombocytopenia (%)	26 (7)	7 (8)	10 (11)	14 (16)	28 (33)	59 (17)
Median AUC		70.7	107	139	195	123
(Range)		(34.9-87.1)	(87.3-123)	(123-158)	(159-516)	(34.9-516)

(Source: Ixazomib exposure-response report, Table 4.e., page 23)

Table 26. Estimated Odds Ratio (95% CI) for the Exposure-Safety Analysis of ≥Grade 3 Hematological Adverse Events

	Odds Ratio[a]	p-value
Anemia	1.007 (1.002, 1.013)	0.0117
Neutropenia	1.000 (0.995, 1.006)	0.8734
Thrombocytopenia	1.013 (1.008, 1.018)	<0.0001

(Source: Ixazomib exposure-response report, Table 4.f., page 26)

Table 27 summarizes non-hematological adverse events by ixazomib exposure quartile. **Table 28** summarizes the estimated odds ratio for those events. As shown in the tables, diarrhea, nausea, vomiting and rash show significant relationships with ixazomib exposure.

Table 27. Summary of ≥Grade 2 Non-hematological AEs by Ixazomib Exposure Quartile as Compared to the Placebo Regimen

	Placebo+ LenDex N=360	Ixazomib Exposure Quartile (ng•hr/mL/day)				
		1st Quartile N=87	2nd Quartile N=87	3rd Quartile N=87	4th Quartile N=86	Total N=347
Diarrhea (%)	53 (15)	9 (10)	15 (17)	12 (14)	34 (40)	70 (20)
Median AUC		72.5	107	139	195	123
(Range)		(34.9-88.8)	(89.1-123)	(124-161)	(162-420)	(34.9-420)
Fatigue (%)	49 (14)	11 (13)	6 (7)	8 (9)	15 (17)	40 (12)
Median AUC		72.1	106	138	191	122
(Range)		(36.6-87.1)	(87.3-122)	(122-157)	(157-430)	(36.6-430)
Nausea (%)	24 (7)	2 (2)	4 (5)	5 (6)	10 (12)	21 (6)
Median AUC		72.1	105	137	185	122
(Range)		(34.9-87.0)	(87.1-122)	(123-156)	(156-344)	(34.9-344)
Peripheral Neuropathy (%)	26 (7)	8 (9)	6 (7)	9 (10)	12 (14)	35 (10)
Median AUC		70.3	105	137	185	120
(Range)		(34.9-87.1)	(87.1-120)	(120-155)	(155-444)	(34.9-444)
Rash (%)	25 (7)	2 (2)	9 (10)	5 (6)	33 (38)	49 (14)
Median AUC		72.5	107	145	214	124
(Range)		(29.1-88.7)	(89.3-124)	(125-167)	(168-679)	(29.1-679)
Vomiting (%)	11 (3)	8 (9)	1 (1)	3 (3)	10 (12)	22 (6)
Median AUC		70.3	105	136	185	120
(Range)		(34.6-86.2)	(86.2-120)	(120-156)	(156-493)	(34.6-493)

(Source: Ixazomib exposure-response report, Table 4.h., page 28)

Table 28. Estimated Odds Ratio (95% CI) for the Exposure-Safety Analysis of ≥Grade 2 Non-hematological AEs

	Odds Ratio[a] (95% CI)	p-value
Diarrhea	1.012 (1.007, 1.017)	<0.0001
Nausea	1.012 (1.004, 1.019)	0.0019
Peripheral neuropathy	1.006 (1.000, 1.012)	0.0495
Rash	1.020 (1.014, 1.026)	<0.0001

(Source: Ixazomib exposure-response report, Table 4.k., page 36)

Reviewer's comments: *The applicant's analyses appear to be reasonable and well aligned with the proposed dose modification scheme based on safety endpoints except gastrointestinal toxicities such as diarrhea. The proposed labeling indicates adjusting dose is needed for gastrointestinal toxicities but the direction is not clearly laid out in the dose modification scheme. Inclusion of dose modification scheme for gastrointestinal toxicities in the labeling is recommended.*

4 REVIEWER'S ANALYSIS

4.1 Introduction

The purpose of the analysis is to evaluate the applicant's analysis and the proposed dose modification. Additionally, the effect of renal function on PFS identified by the statistics reviewer was further evaluated in conjunction with the potential effect of renal function on ixazomib exposure, which was unlikely based on the pharmacokinetics characteristic of the drug.

4.2 Objectives

Analysis objectives were:

1. To evaluate the applicant's exposure-response analysis for efficacy and safety to justify the proposed dose and the dose modification scheme
2. To evaluate the apparent effect of creatinine clearance on PFS

4.3 Methods

Exposure (daily AUC) was estimated in each individual using post-hoc estimates of individual clearance using population PK analysis and actual dose given to the individual. Cumulative dose given to the individual up to the day an event occurred was divided by estimated clearance (CL/F) and then averaged by day.

4.3.1 Datasets

Data sets used for the analysis are summarized in **Table 29**.

Table 29. Datasets for analyses

Study Number	Name	Link to EDR
Population PK	mln9708-pk-20150331-csv.xpt	\\cdsesub1\evsprod\NDA208462\0000\m5\datasets\pop-pk\analysis\legacy\datasets
Exposure-response analysis	ader.xpt	\\cdsesub1\evsprod\NDA208462\0000\m5\datasets\exposure-response analysis\analysis\legacy\datasets
Safety data	adae.xpt	\\cdsesub1\evsprod\NDA208462\0000\m5\datasets\iss\analysis\legacy\datasets
Updated PFS data (submitted on Oct 9, 2015)	adtte xpt	\\cdsesub1\evsprod\NDA208462\0021\m5\datasets\c16010\analysis\legacy\datasets

4.3.2 Software

NONMEM (version 7.3) was used for post-hoc estimates of individual parameters including clearance (CL) and bioavailability (F). R (version 2.13) was used for statistical and graphical analyses.

4.4 Results

4.4.1 Exposure-response for efficacy

Cox-regression analysis showed no significant relationship between ixazomib daily AUC and progression-free survival (**Figure 20**, p-value=0.4 with 1st interim data; **Figure 21**, p-value=0.31 with 2nd interim data). There are no notable differences in baseline risk factors by exposure quartile (Q1, Q2, Q3 and Q4 where Q4 is the highest quartile) of ixazomib daily AUC as shown in **Figure 22.** The distribution of risk factors by exposure quartile with 2nd interim data also showed similar profiles (not shown).

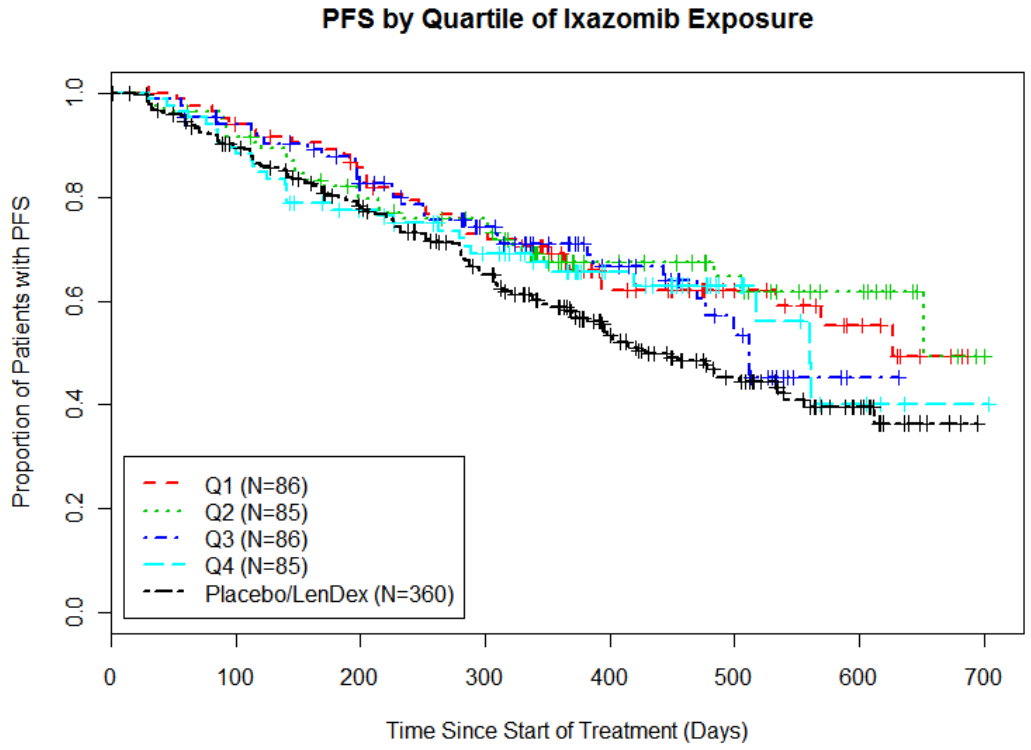


Figure 20. Progression free survival by ixazomib daily AUC quartile . Q1 is the lowest and Q4 is the highest quartile of the exposure (Q1: 33.5-84.2 ng*L/hr, Q2:84.8-117.3 ng*L/hr, Q3: 117.3-147.5ng*L/hr, Q4: 147.8-276.4 ng*L/hr), LenDex is the lenalidomide/dexamethasone active control arm. The analysis was performed with 1st interim data for PFS where an event for PFS was reported in days. Thus the exact day for an event was utilized for time-averaged daily AUC.

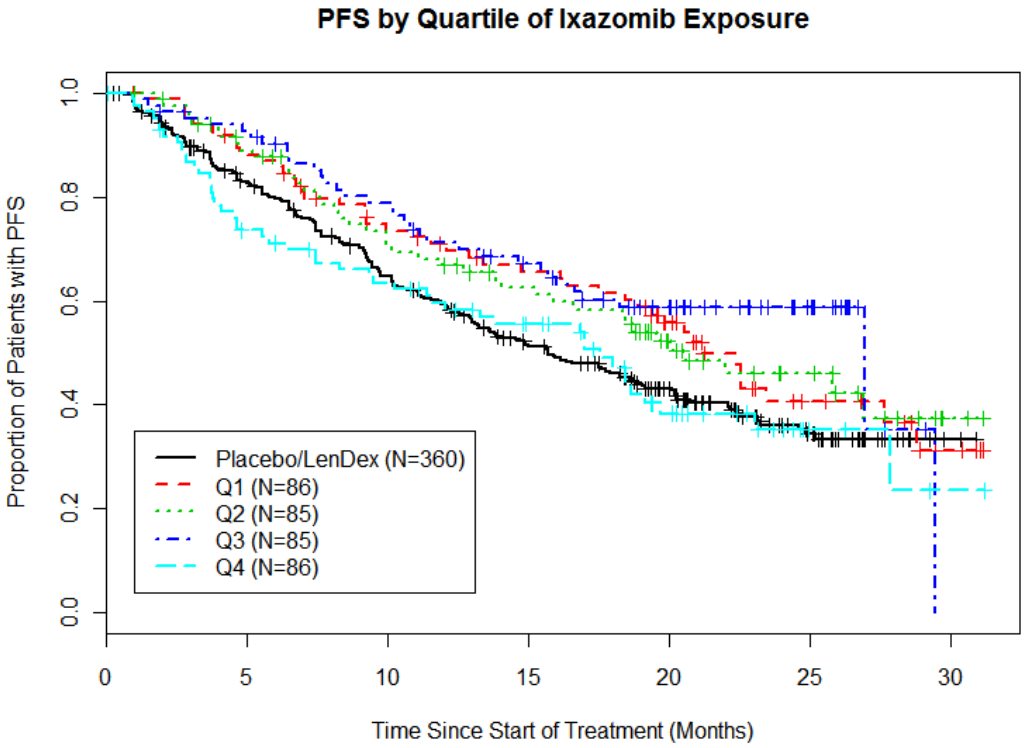


Figure 21. Progression free survival by ixazomib daily AUC quartile . Q1 is the lowest and Q4 is the highest quartile of the exposure (Q1: 10.0-69.0 ng*L/hr, Q2:69.5-97.4 ng*L/hr, Q3: 97.8-132.2 ng*L/hr, Q4: 132.9-260.3 ng*L/hr), LenDex is the lenalidomide/dexamethasone active control arm. The analysis was performed with 2nd interim data for PFS (submitted on Oct 9, 2015) where an event for PFS was reported in months. Thus time-averaged daily AUC was calculated by dividing time-averaged monthly AUC by 30 days.

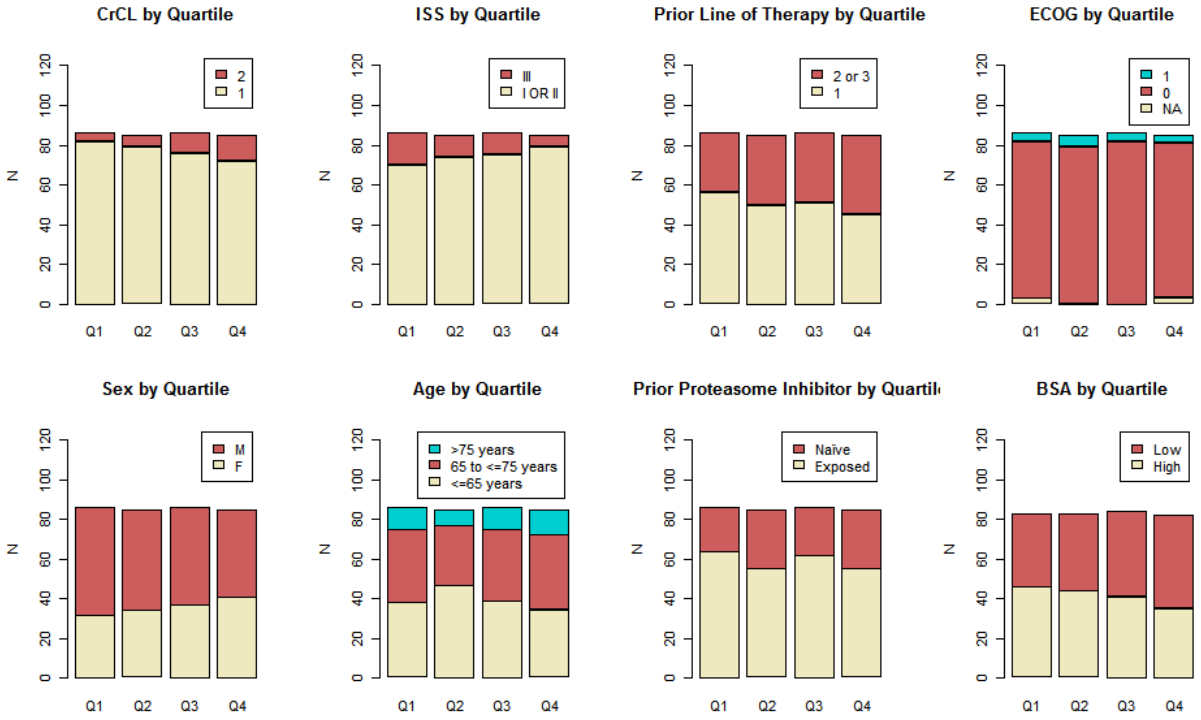


Figure 22. Distribution of patients in each quartile of ixazomib exposure by baseline risk factors

4.4.2 Exposure-response for safety

Exposure-response analyses for safety were conducted for various AEs including ≥Grade 3 hematologic AEs (Thrombocytopenia, Anemia, Neutropenia), and ≥Grade 2 non-hematologic AEs (Rash, Diarrhea, Vomiting, Nausea, Peripheral Neuropathy, Fatigue). Among those endpoints, thrombocytopenia, anemia and rash show steeper exposure-response relationships.

The univariate logistic regression show that increasing ixazomib daily AUC was a significant predictor of increasing probability of having thrombocytopenia (**Figure 23**, p-value $<6.88 \times 10^{-7}$) , rash (**Figure 24**, p-value $<2.59 \times 10^{-10}$) or diarrhea (**Figure 25**, p-value $<2.74 \times 10^{-7}$). The model-predicted probability curve is reasonably aligned with the observed event rates in patients with various quartile of exposure indicating that the model described the data reasonably well.

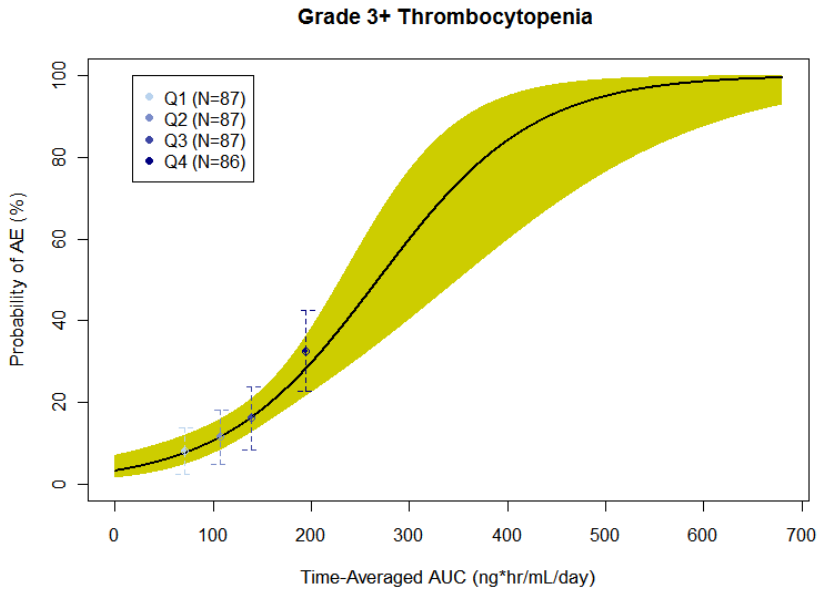


Figure 23. Probability of greater than Grade 3 thrombocytopenia vs. average daily AUC of ixazomib. The olive color shaded region represents the 95% confidence interval (CI)

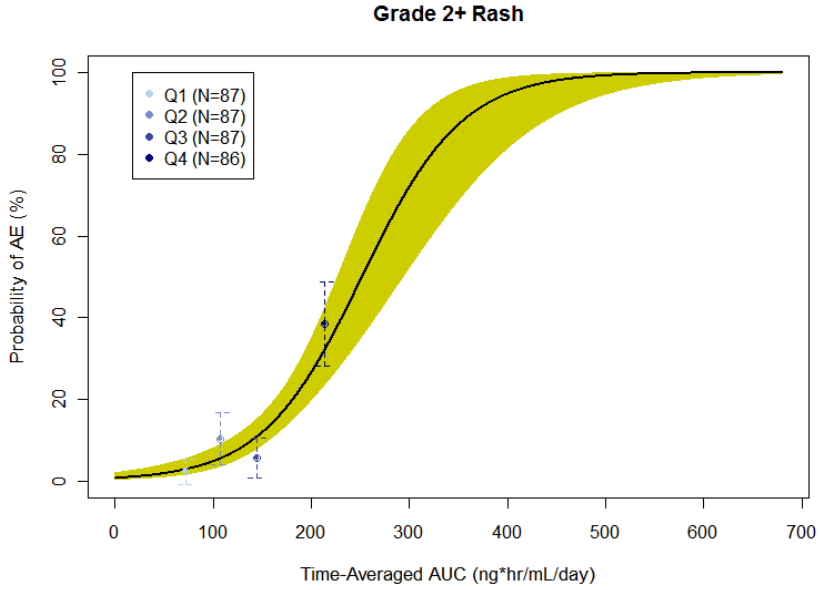


Figure 24. Probability of greater than Grade 2 rash vs. average daily AUC of ixazomib. The olive color shaded region represents the 95% confidence interval (CI).

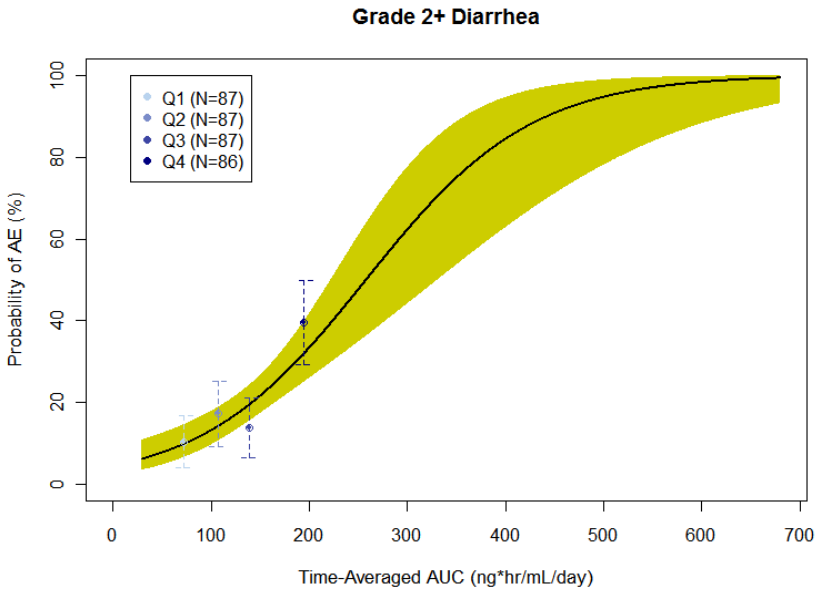


Figure 25. Probability of greater than Grade 2 diarrhea vs. average daily AUC of ixazomib. The olive color shaded region represents the 95% confidence interval (CI).

Logistic regression analyses for greater than Grade 2 nausea and/or vomiting and for greater than Grade 2 peripheral neuropathy also show similar relationships with ixazomib exposures (plots are not shown), which indicate the need for dose modification based on these safety endpoints as well. The univariate logistic regression show that increasing ixazomib daily AUC was also a significant predictor of increasing probability of having anemia (p-value =0.0117). However, the relationship was less steep and the event rate observed in Placebo+LenDex group was even higher than those in patients with 3 lower quartiles of ixazomib exposure (**Figure 26**). These results indicate that the need for dose modification based on anemia is not necessary.

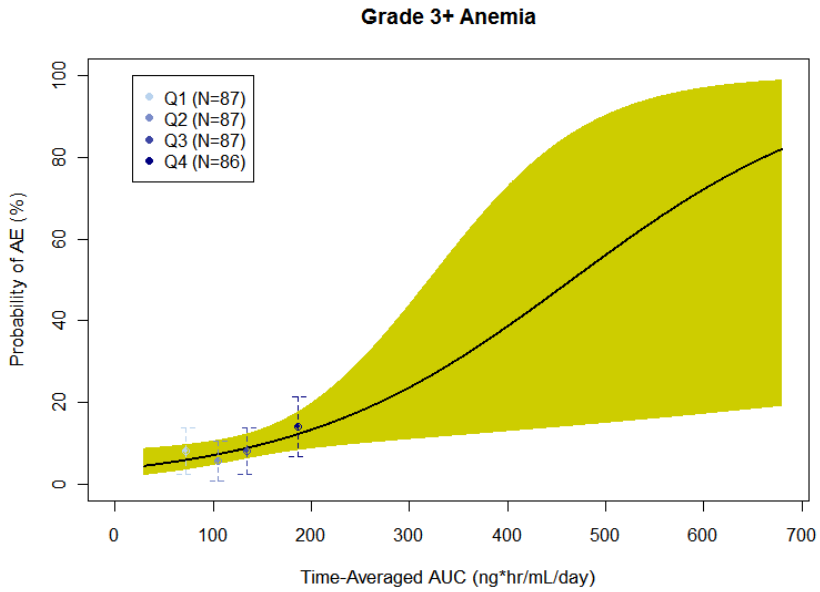


Figure 26. Probability of greater than Grade 3 anemia vs. average daily AUC of ixazomib. The olive color shaded region represents the 95% confidence interval (CI).

4.4.3 Potential effect of CrCL on PFS

There was an apparently significant difference in PFS by Region, Prior Therapy and CrCL (≥60 mL/min vs. <60 mL/min). To evaluate a potential effect of those identified covariates on ixazomib PK, boxplots were generated.

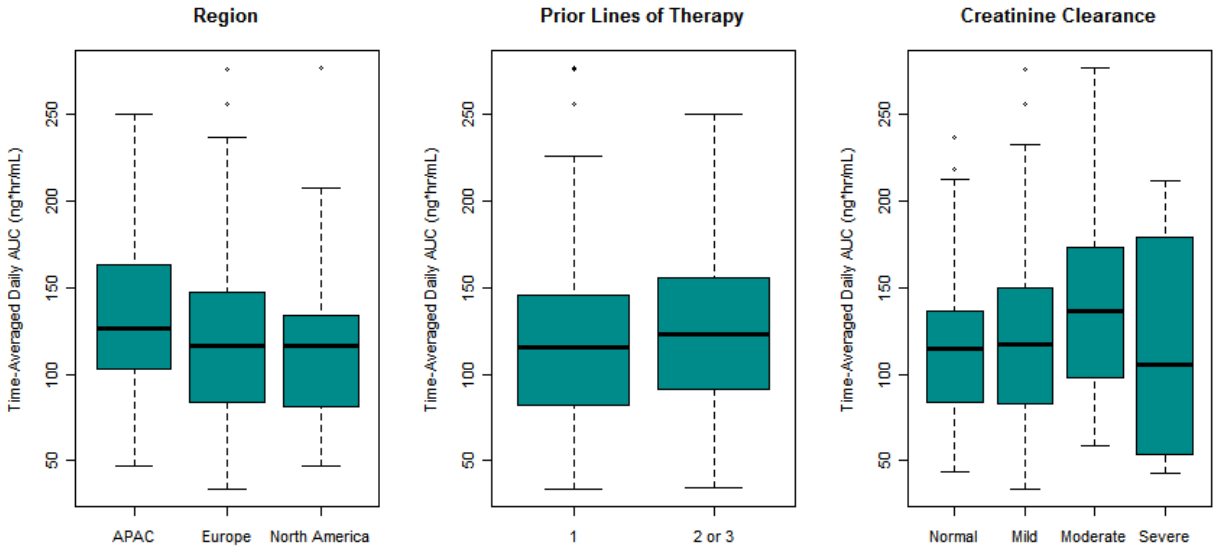


Figure 27. Boxplots for average daily AUC of ixazomib by Region, Number of prior lines of therapy, and Creatinine Clearance.

As shown in **Figure 27**, there are no differerences in ixazomib exposure by those covariates. Considering the fact that only 3% of ixazomib is excreted in urine as unchanged drug, any significant effect of renal function on ixazomib disposition is not expected. The findings were consistent with analysis for ISS.

As shown in **Figure 18**, the difference in PFS by CrCL is in agreement with the difference in PFS by ISS. The patients with renal impairment tend to be sicker at baseline and highly correlated with the ISS status. It is well known that ISS status is highly correlated with survival as well. As expected, higher proportion of patients with ISS stage 3 were included in the group with CrCL <60mL/min (Figure 5).

Additionally, Ixazomib dose was investigated to evaluate potential selective effect of ixazomib by renal impairment. The cumulative dose of ixazomib up to the day of the event gets lower as the renal function becomes deteriorated. This is because the event occurred earlier so the cumulative dose became smaller. The weekly average dose, however, was quite similar across the groups of patients.

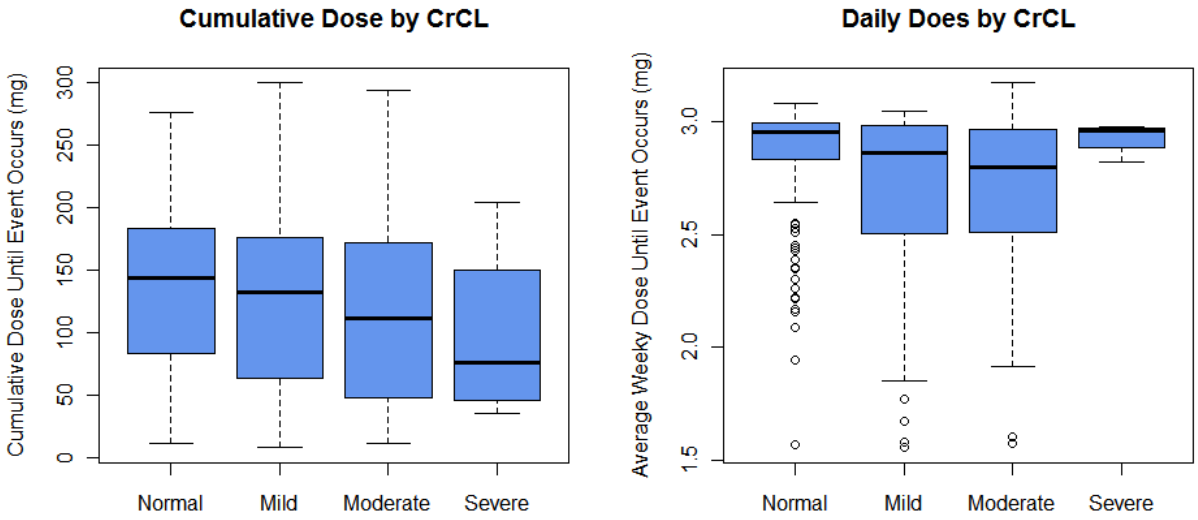


Figure 28. Boxplots for ixazomib dose by CrCL. Left panel shows cumulative dose up to the event and right panel shows averaged weekly dose up the event.

Therefore, the apparent effect of renal function on PFS does not appear to be associated with ixazomib treatment but may be due to differences in the baseline disease condition among CrCL subgroups.

4.4.4 Time to First Dose Reduction

Cox proportional hazards model indicates that ixazomib exposure was not a predictor of time to first dose reduction (**Figure 29**, p-value=0.069). At least 1 dose modification of ixazomib occurred in 81% of patients receiving ixazomib+LenDex (77% of patients receiving placebo+LenDex group) and at least 1 dose modification of lenalidomide occurred in 86% of patients receiving

ixazomib+LenDex (80% of patients receiving placebo+LenDex). After the median number of treatment cycles (12 cycles), 80% of patients in the ixazomib+LenDex continued the starting dose of 4 mg without dose reduction, with 20% of patients having ≥1 dose reduction and 3% of patients having ≥2 dose reductions.

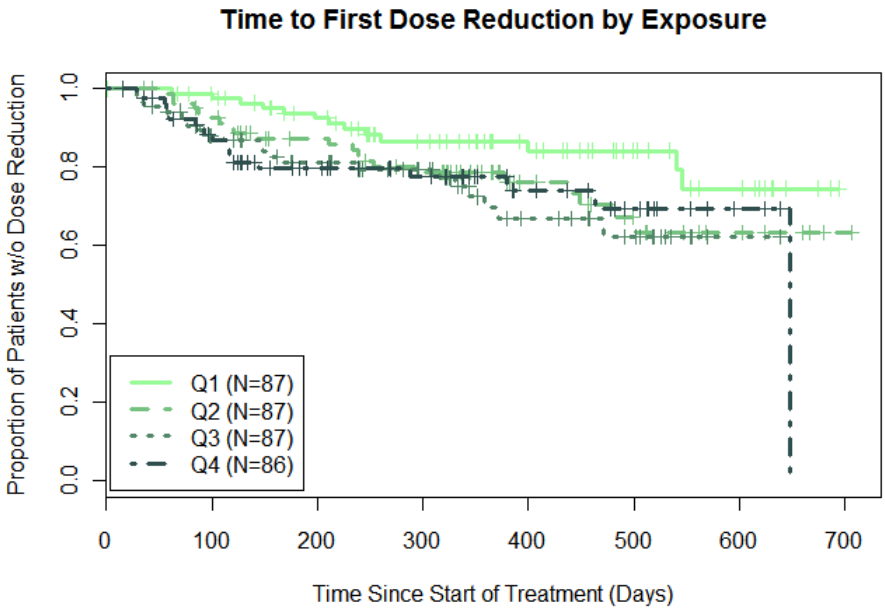


Figure 29. Time to first dose reduction ixazomib daily AUC quartile . Q1 is the lowest and Q4 is the highest quartile of the exposure (Q1: 33.5-84.2 ng*L/hr, Q2:84.8-117.3 ng*L/hr, Q3: 117.3-147.5ng*L/hr, Q4: 147.8-276.4 ng*L/hr), LenDex is the lenalidomide/dexamethasone active control arm

3.2 POPULATON PHARMACOKINETICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRICS REVIEW:

POPULATION PHARMACOKINETICS

NDA/SDN	NDA 208462
Generic Name	Ixazomib
Receipt Date	1st Interim: July 10, 2015; 2nd Interim: October 9, 2015
Proposed Indication	Treatment of patients with multiple myeloma who have received at least one prior therapy
Dosage Form (Strengths)	Capsules (4.0, 3.0, 2.3 mg)
Route of Administration	Oral
Dosing Regimen and Strength	4 mg on Days 1, 8 and 15 of a 28-day cycle
Applicant	Millennium Pharmaceuticals, Inc.
OND Division	Division of Hematology Products
OCP Divisions	Division of Clinical Pharmacology V Division of Pharmacometrics
Pharmacometrics Reviewer	Dinko Rekic, Ph.D.
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.

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1 SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions:

1.1 Are labeling recommendations of no dose adjustments of ixazomib when administered concomitantly with strong CYP1A2 inhibitors appropriate?

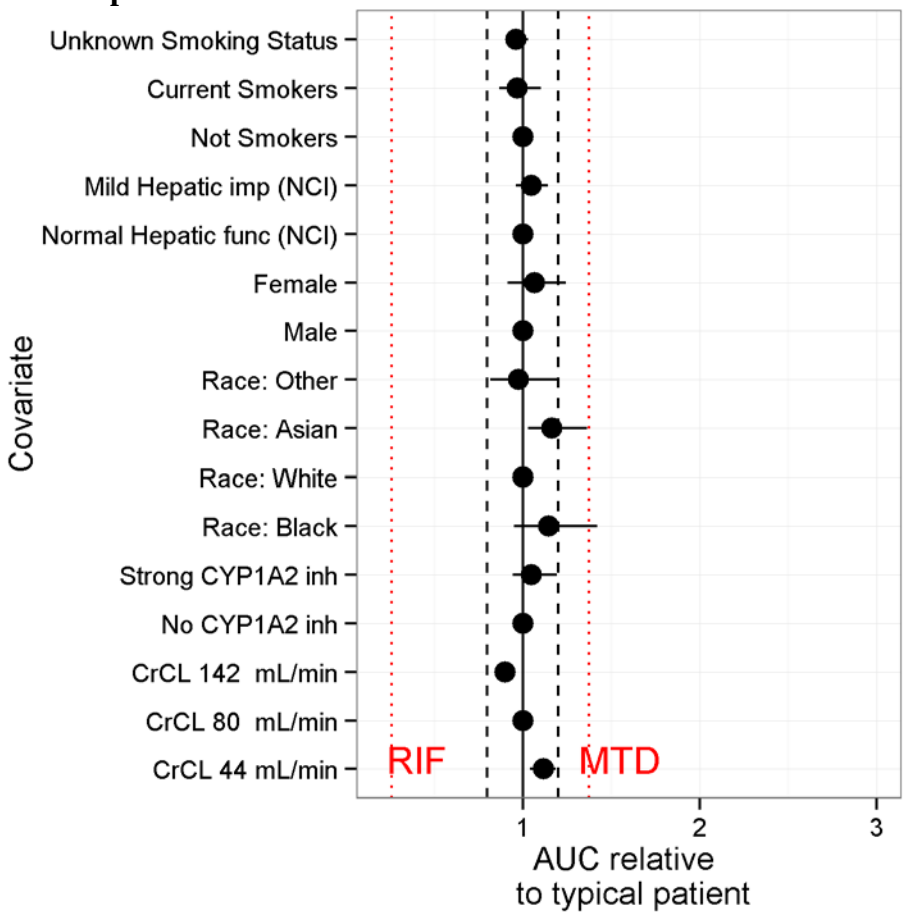
Yes. Applicant's recommendations for not making any dose adjustments with concomitant strong CYP1A2 inhibitors are acceptable because CYP1A2 does not constitute a major metabolic pathway and therefore strong CYP1A2 inhibitors are not expected to cause a clinically significant increase in exposure. These conclusions are supported by a population PK analysis where the estimated effect size of strong CYP1A2 inhibitors on ixazomib exposure is small and statistically insignificant. Additional support is provided by the lack of effect of strong CYP3A4 inhibitors on ixazomib exposure in standalone dedicated clinical pharmacology DDI studies (CYP3A4 is believed to be the main metabolizing CYP enzyme). See section 2.4.2.8 in clinical pharmacology QBR by Dr. Hsu for more information and rationale for this decision.

There is no dedicated clinical pharmacology trial to evaluate the effect of concomitant effect of CYP1A2 inhibitors on the PK of ixazomib. The applicant made the labeling recommendations based on an estimate of 9% higher ixazomib AUC (95% CI of 6-12%) for patients receiving strong CYP1A2 inhibitors (n=20) compared to those not receiving strong CYP1A2 inhibitors (n=735) from a population PK analysis of 10 clinical trials. Reviewer's own analysis of applicant's data estimates a 4.7% (95% CI: [-6;19.2]) increase in exposure due to concomitant strong CYP1A2 inhibitors. Both the reviewer's and the applicant's analysis support the recommendation not to change the dose due to concomitant CYP1A2 inhibitors. Effects of covariates (including strong CYP1A2 inhibitors) on ixazomib exposure as determined by the applicant and the reviewer are shown in **Figure 30.**

The available PK data in individuals with concomitant strong CYP1A2 inhibitors is shown in **Figure 31**. Out of the 27 individuals that where flagged to be on strong CYP1A2 inhibitors, only 20 had measured ixazomib concentrations with concomitant CYP1A2 inhibitor. The population PK dataset included 33 patients who were current smokers. Based on reviewer's analysis as well as the applicant's analysis, smoking does not affect ixazomib exposure (AUC is estimated to be 3.2% (95% CI: [-13.3;10.3]) lower in smokers compared to nonsmokers), **Figure 30.** This further supports the conclusions that CYP1A2 plays a minor role in the metabolism of ixazomib.

In conclusion, we agree with applicant's labeling recommendations regarding effect of concomitant CYP1A2 inhibitors on ixazomib PK. These conclusions are further supported by the in vitro data and clinical DDI studies with strong CYP3A4 inhibitors. CYP1A2 does not appear to contribute to ixazomib metabolism in a significant manner. Therefore, effect of strong CYP1A2 inhibitors on PK of ixazomib is not expected.

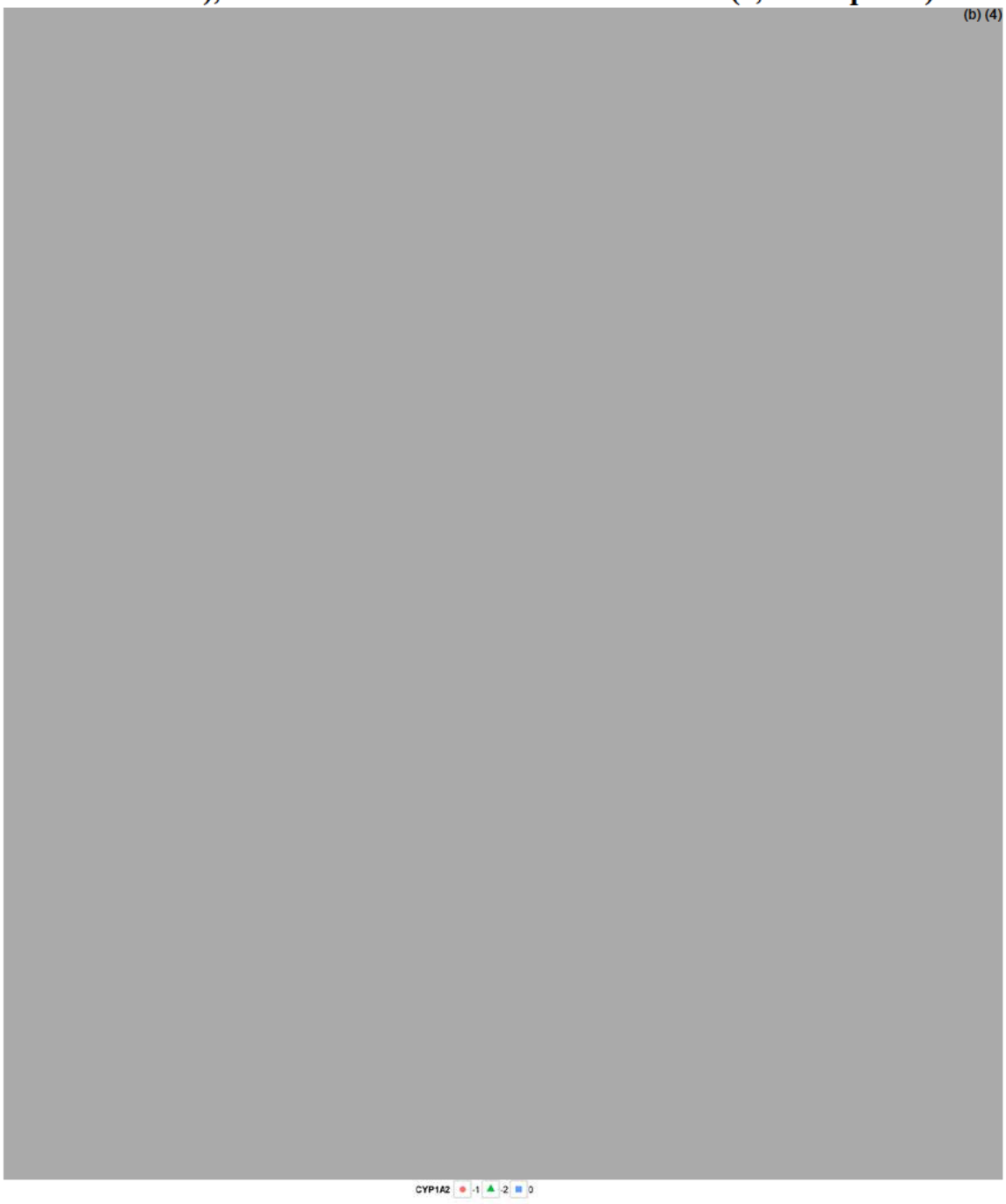
Figure 30. Estimated effect on covariates on ixazomib exposure based on reviewer's analysis including the NCI criteria for hepatic impairment.



Note: Estimated influence of covariates on ixazomib area under the curve (AUC). Circles and lines are estimates of the mean effect and 95% confidence interval (CI); The black horizontal lines represent no change and ±20% change in AUC. The red vertical lines represent reviewer's estimates of the boundaries of therapeutic exposure. The lower line is based on the observed effect of rifampicin (RIF) on ixazomib from study C16009, (0.26 [0.18-0.37]). The higher line is based on the estimated exposure at the maximum tolerated dose (MTD), of 5.5 mg, estimated by dose proportionality principles. Estimated exposures are relative to the typical patient. The typical patient was a white 65 year old man with a BSA of 1.87 m^2, 83.5 ml/min creatinine clearance, with normal hepatic function based on NCI criteria, and not taking concomitant CYP1A2 inhibitors. Combinations of several covariate characteristics may result in higher exposure than what is seen in the plot.

Source: Model: run28.mod
Dataset: MLN9708_PK_20150331.csv
R script: run28_sim_uncert.R

Figure 31. Concentration time profile in subjects on strong CYP1A2 inhibitors (-2, green triangles), on moderate CYP1A2 inhibitors (-1, red circles), and off concomitant CYP1A2 modulators (0, blue squares).



Source: Data: MLN9708_PK_20150331.csv, R code: Summary_of_PK.R

1.2 Is there a need for a BSA based dosing schedule for ixazomib?

No, there is no need to adjust the dose based on patients' BSA. Applicant's analysis concludes that

BSA is not a statistically significant covariate on CL, **Table 35.** Furthermore, **Figure 36** shows that there is no apparent correlation between BSA and CL. Applicant's effect of BSA on ixazomib is shown in **Table 32**. This analysis was based on 755 subjects, with the mean BSA (range) of 1.87 (1.23, 2.67 m^2).

1.3 Is there a need for dose adjustment in patients with mild hepatic impairment?

No, there is no need of dose adjustment in patients with mild hepatic impairment. A dedicated clinical pharmacology trial was conducted to evaluate the effect of moderate and severe hepatic impairment on the PK of ixazomib while the effect of mild hepatic impairment on PK of ixazomib was estimated using population PK analysis. Eighty-three subjects where identified to have mild hepatic impairment based on the NCI-ODWG criteria. Ixazomib AUC was estimated to be 1.05 fold (0.96-1.14) higher in patients with mild hepatic impairment compared to the typical patient. A comparison of effect size and dosing recommendations for patients with mild, moderate and severe hepatic impairment is shown in **Table 30.**

Table 30. Influence of hepatic impairment on ixazomib exposure (AUC)

Patient Category	Mean Ratio (90% CI) versus normal	Labeling Recommendation
Severe hepatic impairment [1] (Study C16018) N=18	1.23 (0.66-2.29)	Lower starting dose of 3 mg
Moderate hepatic impairment [1] (Study C16018) N=13	1.32 (0.70-2.50)	Lower starting dose of 3 mg
Mild hepatic impairment [1] PopPK analysis[3] N=83	1.05[2] (0.96- 1.14)	No dose adjustment

[1]*Definition of hepatic impairment, mild : 1-1.5 x ULM or AST>ULM, moderate: Total bilirubin >1.5–3 x ULN, any AST level, severe: >3 x ULN and any AST level.*
[2]*Estimated by the reviewer using the full covariate model approach. Typical individual is defined in* **Figure 31**
[3]*Model: run28.mod, Dataset: MLN9708_PK_20150331.csv, R script: run28_sim_uncert.R*
Source: Summary of Clinical Pharmacology, Table 2aa.

1.4 Are applicant's recommendations regarding no dose adjustment of ixazomib in patients with mild and moderate renal impairment appropriate?

Yes, the applicant's recommendation of not to change the dose in patients with mild and moderate renal impairment is appropriate. The estimated effect size of CrCL was small as seen in **Table 31** and **Figure 30**. A comparison of the estimated effect size of CrCL on ixazomib exposure for patients with end stage renal disease, severe, moderate, and mild renal impairment is shown in **Table 31.** Furthermore, these recommendations are in line with the ADME properties of ixazomib where it is estimated that ~3% of ixazomib is eliminated unchanged in urine.

Effect of severe renal impairment and end-stage renal disease on PK of ixazomib was evaluated in a dedicated clinical pharmacology trial while population PK analysis was utilized to estimate the effect of mild and moderate renal impairment on PK of ixazomib. Addition of CrCL as a covariate

on CL was statistically significant **Table 35**. The population PK analysis that supports this labeling statement was based on PK samples from 58 patients with moderate renal impairment and 292 patients with mild renal impairment. This sample size is larger then what is typically observed in dedicated standalone clinical pharmacology trials.

Table 31. Influence of renal impairment on ixazomib exposure (AUC)

Patient Category	Mean Ratio (90% CI) versus normal	Labeling Recommendation
End stage renal disease (Study C16015) N=6	1.34 (0.78-2.31)	Lower starting dose of 3 mg.
Severe renal[1] impairment (Study C16015) N=14	1.39 (0.88-2.20)	Lower starting dose of 3 mg.
Moderate renal impairment PopPK analysis CrCL: 45 mL/min N=58	1.14[2] (1.05- 1.17)	No dose adjustment
Mild renal impairment PopPK analysis CrCL: 75 mL/min N=292	1.01[2] (0.977-1.05)	No dose adjustment

[1]Severe renal impairment: CrCL <30 mL/mil; Moderate renal impairment <≤30-<60; Mild renal Impairment ≤60-<90 mL/min.
[2]Estimated by the reviewer using the full covariate model approach, run28.mod. Here a patient with CrCL of 75 or 45 mL/min is compared to the typical individual with CrCL of 80 mL/min. Typical individual is defined in **Figure 31**
Source: Summary of Clinical Pharmacology, Table 2.w

1.5 Are applicant's labeling recommendations of no dose adjustment based on sex and age appropriate?

Yes, sex or age does not affect ixazomib exposure (AUC) in a clinically significant manner and thus dose adjustments are not recommended. Effect size of age and sex is summarized in **Figure 30** and **Table 32**. The population PK analysis that supports these conclusions is based on PK data from 457 males and 330 females. The mean (SD) age was 63 (±10), 396 patients where ≥65 years, 100 patients where ≥75 years, and 7 patients where ≥85 years.

1.6 Are applicant's labeling recommendations regarding race appropriate?

Yes, effect size of race on ixazomib exposure (AUC) is summarized in **Figure 30** and **Table 32**. The population PK analysis that supports the recommendations below is based on PK data from 47 Black, 90 Asian and 627 White patients.

Black versus White

Yes, the influence of race (Black versus White) does not influence ixazomib's exposure (AUC) in a

clinically significant manner.

Asian versus White

Yes, the influence of race (Asian versus White) does not influence ixazomib's exposure (AUC) in a clinically significant manner. The applicant estimates Asian patients to have 35% 95% CI [25; 45] higher AUC compared to White patients. The reviewer's estimate of race effect is somewhat smaller but statistically different from zero, (16.3%, [95% CI: 3.1; 36.2]).

Table 32. Applicant's Labeling Recommendations and Summary of Covariate Effect on Ixazomib Area Under the Curve

Covariate	Action	N, mean, SD, min, max	Applicant's Estimated Effect Size[d] *(AUC % change)*	Reviewers' Estimated Effect Size *(AUC % change)*
Hepatic Impairment[a] Based on Bilirubin Mild	No dose adjustment recommended	Bilirubin (>1-1.5 x ULN[b]): 6 (>1.5 x ULN): 5	5th percentile relative mean -7 [-11;-3] (3 μM) 95th percentile relative mean 12 [6;18] (14 μM)	Not included in the model
Hepatic Impairment NCI criteria Mild	No dose adjustment recommended	NCI Mild: 83	Not included in the model	Mild relative to normal 4.8[-3.9;14]
Renal Impairment[c] (RI) Mild or Moderate	No dose adjustment recommended	Mild: 292 Moderate: 58 Severe: 2 Mean (SD) 90.6 (±32.6) Min 25.8 Max 297	5th percentile relative mean 11 [7;15] (44 mL/min) 95th percentile relative mean -16 [-22;-11] (142 mL/min)	5th percentile relative mean 11.8 [4.1; 18.7] (43.8 mL/min) 95th percentile relative mean -10 [-14.6; -5.4] (142 mL/min)
Strong CYP1A2 Inhibitors	No dose adjustment recommended	Patients on ciprofloxacin: 36	Relative to patients not on ciprofloxacin Strong inhibitor: 9 [6;12]	Relative to patients not on strong CYP1A2 inhibitors 4.9 [-5;7.19]
AGE (years)	No dose adjustment recommended	≥65: 396 ≥75: 100 ≥85: 7 Mean (SD) 63 (±10) Min: 23 Max: 91	5th percentile relative mean -14 [-19;-9] (49 years) 95th percentile relative mean 12 [8;17] (79 years)	Not included in the model
Sex	No dose adjustment recommended	Male: 457 Female: 330	Females relative to males: 13 [6;21]	Females relative to males: 6.7 [-9;24]
BSA (m^2)	No dose adjustment recommended	Mean (SD) 1.87(±0.24) Min: 1.23 Max: 2.67	5th percentile relative mean 16 [11;21] (1.5 m^2) 95th percentile relative mean -16 [-21;-11] (2.25 m^2)	Not included in the model
Race	No dose adjustment recommended	White: 627 Black: 47 Asian: 90 Other: 23	Relative to White Black: 6 [-9;20] Asian: 35 [25;45] Other: -5 [-25;14]	Relative to White Black: 15 [-5.6;42] Asian: 16 [3;36] Other: -2.4 [-18.4;20]

[a] *Upper limit of normal (17.1 μM total bilirubin)*
[b] *Mild impairment is defined as total bilirubin >1-1.5 x ULN by the applicant*
[c] *Mild renal impairment; Creatinine clearance 60-89 mL/min, Moderate renal impairment Creatinine clearance 30-59 mL/min, Severe renal impairment Creatinine clearance 15-29 mL/min*
[d] *Effect size is estimated based on linear regression of post-hoc estimates of individual AUC.*

2 RESULTS OF SPONSOR'S ANALYSIS

The analysis included data from seven Phase 1 studies (C16001, C16002, C16003, C16004, C16007, C16013, and TB-MC010034), two Phase 1/2 studies (C16005, C16008) and one Phase 3 study (C16010), **Table 33**. Applicant's narratives of the trials are listed in **Table 34.**

The applicant developed a population PK model based on the 10 studies listed above. Covariates were selected for inclusion into the final population PK model based on a pre-defined list of relevant parameter-covariate relationships. All covariates were included in the analysis dataset as subject-specific baseline covariates, except CYP-modulatory concomitant drugs which were included as time-dependent covariates. Univariate and multivariate covariates were tested for significance based on the likelihood ratio test and included if they were found to be statistically significant and reduced the corresponding random effect variance by more than 10%. The final model was constructed using a forward-selection ($p<0.01$), backward-elimination method ($p<0.001$).

The observed ixazomib IV and oral plasma concentration data were described by a three compartment model with linear distribution and elimination kinetics, including first order linear absorption with lag time describing the oral dose PK profile. The developed model included log-normally distributed patient-level random effects on systemic clearance (CL), absolute bioavailability of an oral dose (F), and volume of the second peripheral compartment (V4). Residual unexplained variability of the log transformed ixazomib plasma concentration was described by an additive error model with time-varying variance.

Body surface area (BSA) on V4 was included as the only patient covariate in the final model. Inclusion of BSA explained 12.6% of the variability on V4. Patients at the 5th and 95th percentiles of BSA were predicted to have 37% lower and 46% higher V4, respectively, than the median patient. BSA does not impact AUC∞ as BSA was not identified as a covariate on CL.

Other patient covariates, including sex, age, race, mild or moderate renal impairment (creatinine clearance > 30 mL/min), mild hepatic impairment (total bilirubin 1-1.5 times ULN), and smoking status, were not found to impact ixazomib pharmacokinetics, suggesting that no dose adjustment is required based on these covariates. Additionally, there was no effect of either CYP1A2 or CYP3A4-modulatory concomitant drugs (as a time varying covariate) on the PK of ixazomib. Tested covariate-parameter relationships are summarized in **Table 32**. Final parameter estimates are shown in **Table 39.** Selection of goodness of fit plots provided by the applicant is shown in **Figure 32**. Plots of applicant's estimate of covariate effect are also shown in **Figure 33**.
Source: Population PK report, Synopsis

Figure 32. Selected goodness of fit plots provided by the applicant

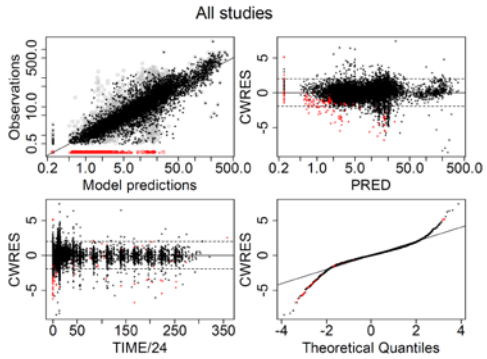


Figure 67: Residual-based diagnostics of the final model, showing data from all studies. Top-left: goodness-of-fit showing observations versus individual (black) and population (gray) predictions. Top-right and bottom-left: CWRES versus population predictions and time (unit: hours). Bottom-right: q-q plot comparing the distribution of CWRES to a normal distribution. Red markers indicate data below the limit of quantification.

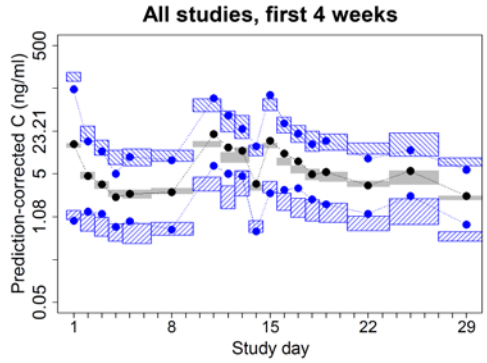
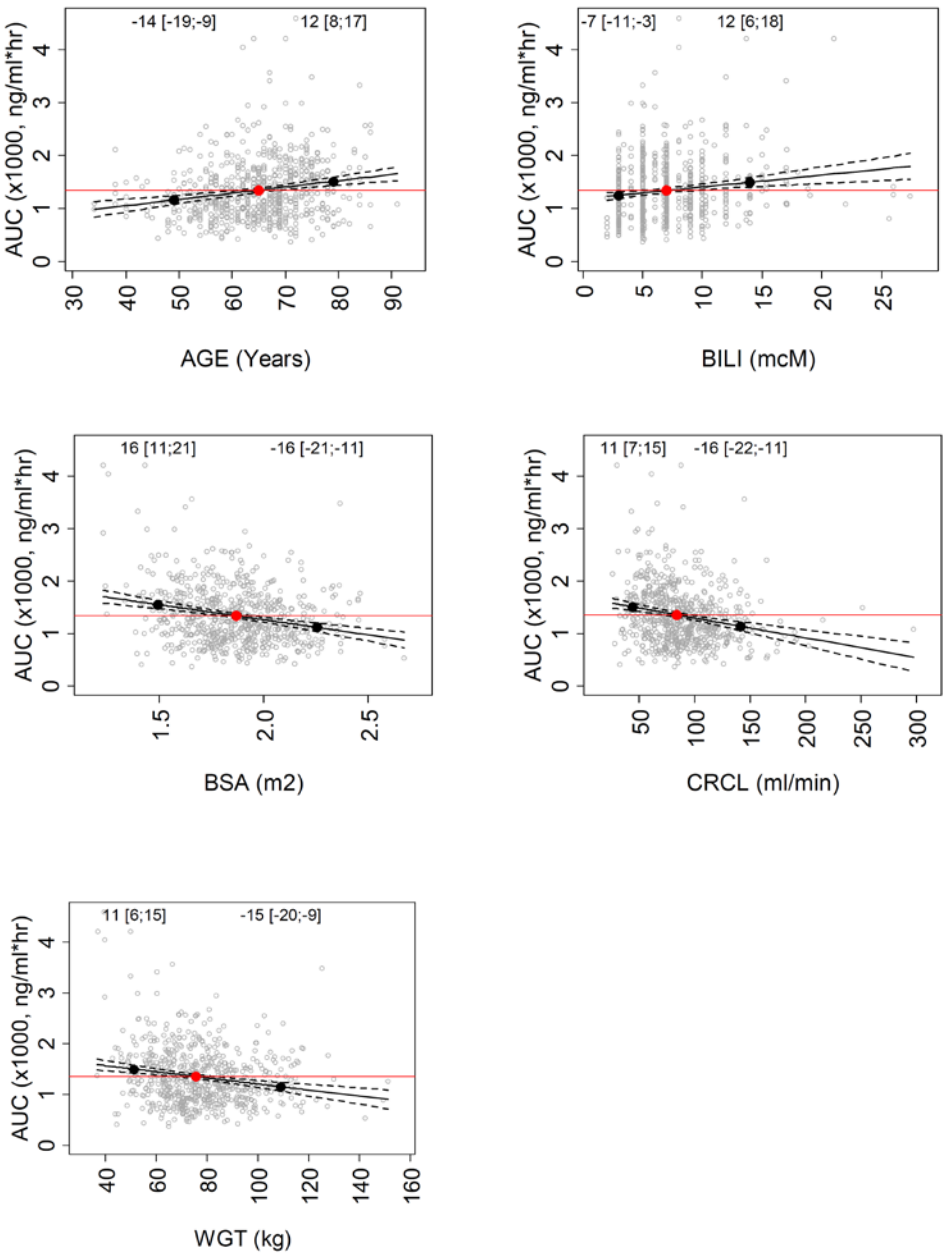


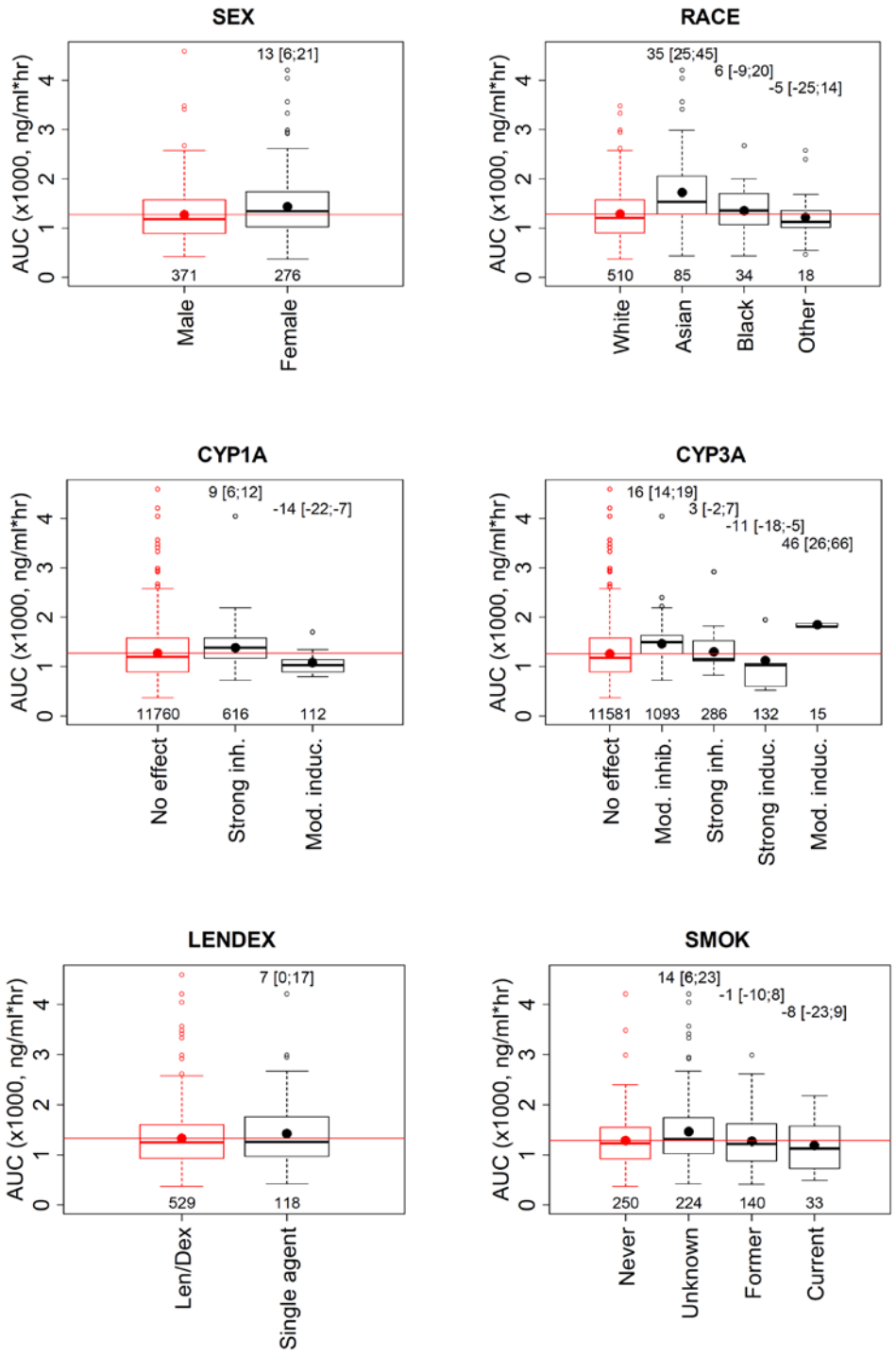
Figure 14: VPC showing data from the first 4 weeks of all studies, based on 1000 simulated datasets, comparing median and 2.5th-97.5th percentile interval of prediction-corrected observed ixazomib concentrations (black and blue dots, respectively) to corresponding model simulations (95% CI, gray and blue hatched areas).

Figure 33. Applicant's estimate of covariate effect



Note: *Correlation 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).*

Source: *Population PK report, figure 21:*



Note: *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. The time-dependent covariates (CYP1A and CYP3A) are stratified by patient days.*

Source: *population PK report, figure 22*

Table 33. Clinical Studies Included in the Population PK Analysis

Study (phase)	Patient population	n[$]	Regimen[#]	Ixazomib dose[%]
C16001 (1)	Patients with advanced non-hematologic malignancies	80	TW, IV, single agent	Dose escalation (0.2-4.8 mg)
C16002 (1)	Patients with lymphoma	28	W, IV, single agent	Dose escalation (0.23-6.8 mg)
C16003 (1)	Patients with relapsed and/or refractory multiple myeloma	52	TW, PO, single agent	Dose escalation (0.4-4.8 mg)
C16004 (1)	Patients with relapsed and/or refractory multiple myeloma	51	W, PO, single agent	Dose escalation (0.2-8.9 mg)
C16005 (1/2)	Patients with newly diagnosed multiple myeloma	62	W, PO, combination with len/dex	Phase 1: Dose escalation (2.9-10.6 mg) Phase 2: 4.0 mg
C16007 (1)	Patients with relapsed or refractory light-chain (AL) amyloidosis	15	W, PO, single agent	Dose escalation (4.0-5.5 mg)
C16008 (1/2)	Patients with newly diagnosed multiple myeloma	63	TW, PO, combination with len/dex	Phase 1: Dose escalation (3.0-3.7 mg) Phase 2: 3.0 mg
C16010 (3)	Patients with relapsed and/or refractory multiple myeloma	347	W, PO, combination with len/dex	4.0 mg
C16013 (1)	East Asian patients with relapsed and/or refractory multiple myeloma	43	W, PO, combination with len/dex	4.0 mg
TBMC010034 (1)	Japanese patients with relapsed and/or refractory multiple myeloma	14	W, PO, single agent or combination with len/dex	4.0 mg

[$]: patients included in the population PK analysis.
[#]: TW: 21-day cycle with doses on days 1, 4, 8, 11; or W: 28-day cycle with doses on days 1, 8, 15, route of administration, and single agent versus combination treatment with len(alidomide)/dex(amethasone).
[%]: numbers in brackets show the range of starting doses administered to patients.

Source: Population PK report, Table 3.

Table 34. Description of trials included in the population PK analysis

Study ID	Trial description
Study C16001	**An Open-Label, Dose Escalation, Phase 1 Study of MLN9708, a Second-Generation Proteasome Inhibitor, in Adult Patients with Advanced Nonhematologic Malignancies** This study was the first to administer ixazomib to humans. The primary study objective was to determine the safety profile, establish the maximum tolerated dose (MTD), and inform the phase 2 dose of ixazomib administered intravenously (IV) in patients with nonhematologic malignancies. A secondary objective was to describe the pharmacokinetics (PK) and pharmacodynamics of IV-administered ixazomib. Ixazomib was administered on Days 1, 4, 8, and 11 of a 21-day cycle
Study C16002	**An Open-Label, Dose-Escalation, Phase 1 Study of MLN9708, A Second-Generation Proteasome Inhibitor, in Adult Patients with Lymphoma** The primary objectives of this study were to determine the safety profile and MTD of ixazomib administered intravenously in patients with lymphoma, and to determine the recommended phase 2 dose of ixazomib in patients with lymphoma. A secondary objective was to characterize the PK of IV-administered ixazomib in plasma and urine. Ixazomib was administered on Days 1, 8, and 15 of a 28-day cycle.
Study C16003	**An Open Label, Dose-Escalation, Phase 1 Study of the Oral Form of MLN9708, a Second Generation Proteasome Inhibitor, in Adult Patients with Relapsed and/or Refractory Multiple Myeloma** The primary study objectives were to determine the safety profile, tolerability, and MTD of ixazomib administered orally in patients with relapsed and/or refractory multiple myeloma, and to inform the recommended phase 2 dose of ixazomib. A secondary objective was to characterize the PK in plasma of ixazomib administered orally. Ixazomib was administered orally on Days 1, 4, 8, and 11 of a 21-day cycle. A 3 + 3 dose escalation scheme was used to determine the MTD and followed a modified Fibonacci sequence to guide escalation with doses of 2.0-, 1.67-, 1.50-, 1.40-, and 1.33-fold over the previous dose level thereafter.
Study C16004	**An Open-Label, Dose-Escalation, Phase 1 Study Evaluating the Safety and Tolerability of Weekly Dosing of the Oral Form of MLN9708, a Second-Generation Proteasome Inhibitor, in Adult Patients with Relapsed and Refractory Multiple Myeloma** The primary study objective was to determine the safety profile, tolerability, and MTD of ixazomib administered orally on a weekly dosing schedule in patients with relapsed and/or refractory multiple myeloma. A secondary objective was to characterize the PK in plasma of ixazomib administered orally. Ixazomib was administered orally on Days 1, 8, and 15 of a 28-day cycle. A 3 + 3 dose escalation scheme was used to determine the MTD and followed a modified Fibonacci sequence to guide escalation with doses of 2.0-, 1.67-, 1.50-, 1.40-, and 1.33-fold over the previous dose level thereafter.
Study C16005	**An Open-Label, Dose-Escalation, Phase 1/2 Study of the Oral Form of MLN9708, a Second-Generation Proteasome Inhibitor, Administered in Combination with Lenalidomide and Low-Dose Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma Requiring Systemic Treatment** The primary objectives of the study were to determine the safety, tolerability, and maximum tolerated dose of oral ixazomib administered weekly in combination with lenalidomide and low dose dexamethasone in a 28-day cycle in patients with newly diagnosed multiple myeloma (NDMM), and to determine the recommended phase 2 dose of the combination of oral ixazomib, lenalidomide, and low-dose dexamethasone. A secondary objective was to characterize the PK in plasma of oral ixazomib in combination with lenalidomide and low-dose dexamethasone. Patients received escalating BSA-based doses (phase 1) or at the RP2D of 4.0 mg (phase 2) of ixazomib orally on Days 1, 8, and 15; plus 40 mg of dexamethasone PO on Days 1, 8, 15, and 22; and lenalidomide 25 mg PO on Days 1 through 21 of a 28-day cycle.

Study C16007	**An Open-Label, Dose-Escalation, Phase 1 Study of the Oral Formulation of MLN9708 Administered Weekly in Adult Patients with Relapsed or Refractory Light-Chain (AL) Amyloidosis Who Require Further Treatment** The primary study objectives were to determine the safety, tolerability, and MTD of oral ixazomib administered weekly in patients with previously treated relapsed or refractory light chain (AL) amyloidosis, and to determine the recommended phase 2 dose (RP2D) of oral ixazomib administered weekly. A secondary objective was to characterize the plasma PK of ixazomib in this patient population. Patients received escalating doses of ixazomib PO on Days 1, 8, and 15 in a 28-day cycle in the absence of disease progression or unacceptable toxicity. If there was no hematologic response (CR + VGPR + PR) after completion of 3 cycles of single-agent ixazomib, dexamethasone was added on Days 1 to 4 of every cycle (Days 1-4 every 28 days) beginning with Cycle 4.
Study C16008	**An Open-Label, Dose-Escalation, Phase 1/2 Study of the Oral Formulation of MLN9708 Administered Twice-weekly in Combination with Lenalidomide and Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma Requiring Systemic Treatment** The primary study objective was to determine the safety, tolerability, MTD, and RP2D of oral ixazomib administered twice-weekly in combination with lenalidomide and low-dose dexamethasone in a 21-day cycle in patients with NDMM. A secondary objective was to characterize the PK in plasma of oral ixazomib in combination with lenalidomide and low-dose dexamethasone. Ixazomib was administered twice-weekly on Days 1, 4, 8, and 11 of a 21-day cycle. Lenalidomide was given daily for 14 days with dexamethasone given on the day of and day after the ixazomib doses in a 21-day cycle.
Study C16010	**A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients with Relapsed and/or Refractory Multiple Myeloma** The primary study objective of this Phase 3 study was to determine whether the addition of oral ixazomib to the background therapy of lenalidomide and dexamethasone improves progression-free survival (PFS) in patients with relapsed and/or refractory multiple myeloma. A secondary objective was to determine the safety of the addition of ixazomib to lenalidomide and dexamethasone. Patients received study drug (ixazomib 4.0 mg or matching placebo capsule) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle.
Study C16013	**A Phase 1 Pharmacokinetic and Tolerability Study of Oral MLN9708 Plus Lenalidomide and Dexamethasone in Adult Asian Patients with Relapsed and/or Refractory Multiple Myeloma** The primary study objective was to characterize the PK in plasma of oral ixazomib in combination with lenalidomide and dexamethasone in Asian patients with relapsed and/or refractory multiple myeloma. All patients received study drug (ixazomib 4.0 mg) on Days 1, 8, and 15 plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle.
TB-MC0 10034	**A Phase 1 Study of MLN9708 in Japanese Patients with Relapsed and/or Refractory Multiple Myeloma** The primary study objective was to evaluate the tolerability, safety, and pharmacokinetics of ixazomib alone or in combination with lenalidomide and dexamethasone in Japanese patients with relapsed and/or refractory multiple myeloma. All patients received study drug (ixazomib 4.0 mg in cohorts 1 [single agent] and 2) on Days 1, 8, and 15, plus lenalidomide (25 mg) on Days 1 through 21 and dexamethasone (40 mg) on Days 1, 8, 15, and 22 of a 28-day cycle (cohort 2).

Source: Applicant's Population PK report

Table 35. Summary of applicant's covariate analysis

Covariate	CL: change in OFV	CL: change in IIV variance (%)	CL: statistical significance (p-value)	V4: change in OFV	V4: change in IIV variance (%)	V4: statistical significance (p-value)
Age (years)	-16.4	0.5	0.0001			
Serum albumin (g/L)	-1.0	0.4	0.3263	-3.1	-0.1	0.0791
Alanine aminotransferase (U/L)	-0.4	-0.4	0.5461			
Aspartate aminotransferase (U/L)	-125.7	1.8	<0.0001			
Total bilirubin (µM)	-131.8	3.3	<0.0001			
Body surface area (m^2)	-3.2	2	0.0720	-153.1	-12.6	<0.0001
Creatinine clearance (mL/min)	-18.6	2.7	<0.0001			
CYP1A2	-1.9	-0.4	0.5932			
CYP3A4	-9.5	-1.8	0.0505			
Hematocrit (proportion of 1)	-1.5	-0.1	0.2264	-0.6	-0.7	0.4299
Hemoglobin (g/L)	-2.4	-0.4	0.1232	-2.9	-1.7	0.0873
Route of administration	-7.2	-2.6	0.0075			
Len/dex combination	-141.5	-4.5	<0.0001			
Dosing regimen	-122.0	1.9	<0.0001			
Race	-29.0	2.8	<0.0001			
Sex	-2.7	0.8	0.0992	-124.4	-0.5	<0.0001
Smoking status	-0.7	0.7	0.8730			
Body weight (kg)	0.0	0.2	0.8710	-152.3	-11.6	<0.0001

Source: Applicant's Population PK report, Table 14.

Reviewer's comments
The applicant included only covariates that met the statistical criteria described above and reduced the BSV by 10%. BSA was the only covariate able to meet both the criteria. Usually covariate inclusion is only based on statistical significance e.g. stepwise covariate modeling. Another method is the full covariate approach where all covariates of interest are included in the model and their effects are estimated. This reviewer is of the opinion that the applicant's covariate inclusion criterion is too stringent and is not commonly used.

Although only one covariate was included in the model, the applicant estimated covariate effects based on linear regression of the individual AUC estimates that are based on EBE estimates of CL and F. This approach is also considered to be unusual. Because the estimated covariate effect is used to inform labeling, an independent covariate analysis was conducted by the reviewers based on the full covariate approach. Results of reviewer's analysis and recommendations are consistent with the applicant's proposal.

It should be noted that the applicant defined hepatic impairment based on bilirubin only and not the established NCI-ODWG criteria for hepatic impairment. The reviewer's analysis uses the NCI-ODWG criterion which is based on bilirubin and AST.

3 REVIEWER'S ANALYSIS

3.1 Introduction

The purpose of this analysis is to verify the applicant's labeling claims that originate from the population PK model. Independent analysis was conducted by the reviewer for the following reasons:

1. Applicant's criteria for inclusion of covariates were stringent resulting in selection of only one covariate (BSA onV4). In addition to the common statistical requirement for covariate inclusion ($p<0.01$), the selected covariate had to reduce the corresponding random effect variance by more than 10%.
2. Applicant did not use the NCI criteria for mild hepatic impairment which uses both AST and total bilirubin levels for classification. Applicant's criteria used only total bilirubin. Based on the NCI criteria, 83 subjects where identified to have mild hepatic impairment versus the 5 subjects that where identified based on the applicant's criteria.

3.2 Objectives

Analysis objectives are:

1. Estimate the effect size of covariate used for labeling and assess need for dose adjustment.

3.3 Methods

The full covariate approach was used for the analysis of covariate effect[1]. Covariates added to the applicant's final model (run1.mod) are shown in **Table 36.** Example NONMEM code for continuous and categorical covariates is shown in **Table 37.**

(b) (4)

Table 36. Covariates added to the applicant's final model

Covariate	Parameter	Models, Covariate type, Comments
CrCL	CL	run28.mod Continuous Centered around median CrCL (80 mL/min)
CYP1A2 inhibitors	CL	run28.mod Time dependent categorical covariate. :
Race	CL	run28.mod Categorical covariate. Categories: White (most common), Black, Asian, Other
Sex	CL	run28.mod Categorical covariate. Categories: Male (most common), female
Hepatic status	CL	Run28.mod Categorical. Categories: normal (most common), mild impairment
Smoking	CL	Run28.mod Categorical. Categories: nonsmokers (most common), smokers, unknown smoking status.

[1] Gastonguay MR. Full covariate models as an alternative to methods relying on statistical significance for inferences about covariate effects: a review of methodology and 42 case studies. Abstract 2229. Paper presented at: Annual Meeting of the Population Approach Group in Europe; 7–10 June 2011; Athens, Greece.

Table 37. Example NONMEM code for inclusion of continuous and categorical covariates

NONMEM code for covariate modeling
Categorical covariates

IF(COV.EQ.0) PARCOV = 1 ; Most common
IF(COV.EQ.1) PARCOV = (1 + THETA(1))
IF(COV.EQ.2) PARCOV = (1 + THETA(2))
IF(COV.EQ.3) PARCOV = (1 + THETA(3))

Continuous covariates
PARCOV =((COV/ median)**THETA(4))

3.3.1 Data Sets

Data sets used are summarized in **Table 38.**

Table 38. Analysis Data Sets

Study Number	Name	Link to EDR
C16001, C16002, C16003, C16004, C16007, C16013, TB-MC010034, C16005, C16008, and C16010	MLN9708_PK_20150331.csv	\\cdsesub1\evsprod\nda208462\0000\m5\datasets\pop-pk\analysis\legacy\datasets\mln9708-pk-20150331-csv.xpt

3.3.2 Software

NONMEM version 7.3 was used for fitting of models; Pirana Version 2.9.0 was used for NONMEM project management, R Studio Version 0.99.467 with R version 3.2.1 was used for data handling, statistical analysis and graphics; PsN was used to run NONMEM and for computational assistance.

3.3.3 Models

Model run28.mod

This model was also based on applicant's final model (run1.mod) and included covariates listed in **Table 7**. This model does not include covariates that with correlation >|0.30|.

3.4 Results

Estimated covariate effect is discussed in Section **1.1** through **1.6.** Forest plot of covariate effect are shown in **Figure 30.**

Final parameter estimates of run28.mod are shown in **Table 39.** Basic goodness of fit plots are shown in **Figure 34.** A representative sample of individual observations and predictions is shown in **Figure 35.** Plots of ETA versus covariates for applicant's final model (run1.mod) and reviewer's full covariate model are shown in **Figure 36**.

Table 39. Parameter estimates based on the reviewer's and the applicant's model

Parameter	Reviewer's full covariate model (NCI) *run28.mod* *OFV: 453.527*		Applicant's final model *run1.mod* *OFV: 516.15*	
	Estimate	*RSE (Shrinkage)*	Estimate	*RSE (Shrinkage)*
KA (h^{-1})	0.35	*8%*	0.34	*8%*
CL (L/h)	1.82	*8%*	1.86	*7%*
V2 (L)	13.74	*4%*	13.7	*4%*
Q3 (L/h)	4.8	*8.0%*	5.18	*7%*
V3 (L)	295.89	*1%*	309	*1%*
Q4 (L/h)	26.31	*2%*	26.1	*2%*
V4 (L)	202.35	*1%*	205	*1%*
F1 (fraction)	0.55	*9%*	0.58	*9%*
SD_1	1.91	*10.0%*	1.90	*11%*
SD_0	0.462	*3.0%*	0.46	*3%*
K_{SD}	0.846	*21%*	0.84	*22%*
TLAG (h)	0.2187	*0%*	0.22	
BSA_V4	2.47	*15%*	2.06	*18%*
CRCL_CL	0.184	*20%*	.	.
sCYP1A2	-0.046	*117%*	.	.
BLACK_CL	-0.127	*70%*	.	.
ASIAN_CL	-0.145	*43%*	.	.
OTHER_CL	0.0287	*326%*	.	.
FEMALE_CL	-0.0593	*129%*	.	.
MILDHEP_CL	-0.0459	*88%*	.	.
CURRENT_SMOKERS_CL	0.0336	*182%*	.	.
UNKNOWN_SMOKERS_CL	0.0406	*85%*		
BSV_CL	44.8%	*5.4%*[1] *(19.9%)*	44%	*11% (13%)*
BSV_F	72.1%	*4.1%*[1] *(12.8%)*	73%	*8% (13%)*
Corr(CL_F)	84.4%	*10.4%*	82%	*11%*
BSV_V4	78.3%	*6.3%*[1] *(36.8%)*	79%	*12% (37%)*

[1] *SD scale*

Figure 34. Basic goodness of fit plots for reviewer's full covariate models

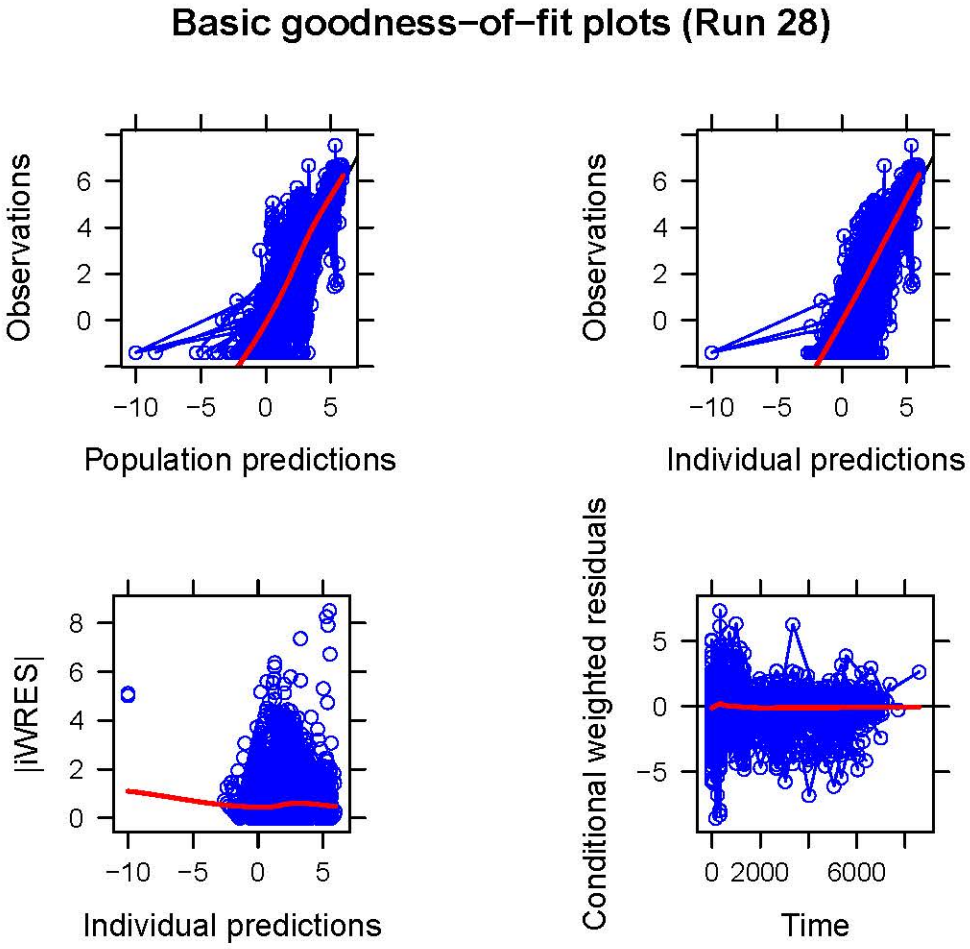


Figure 35. Representative sample of individual observations and predictions versus time

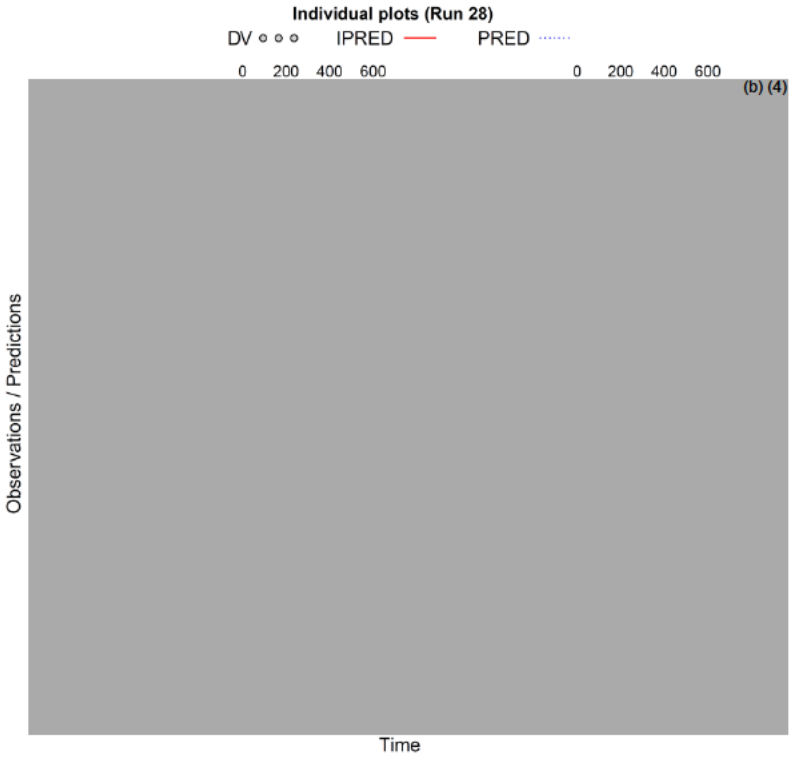
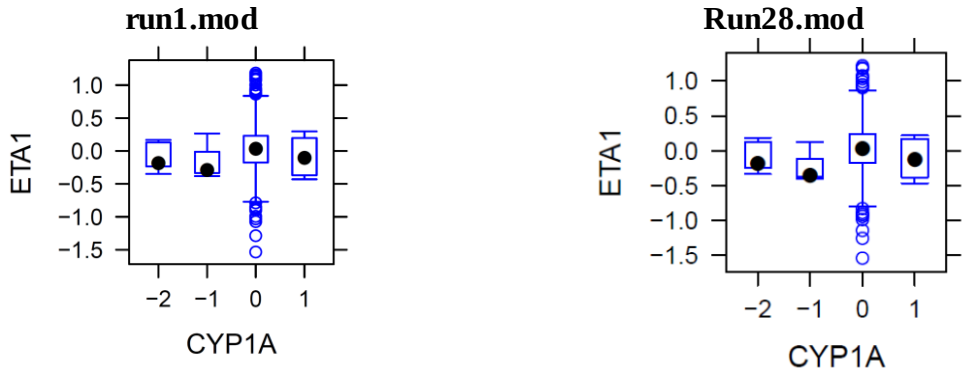
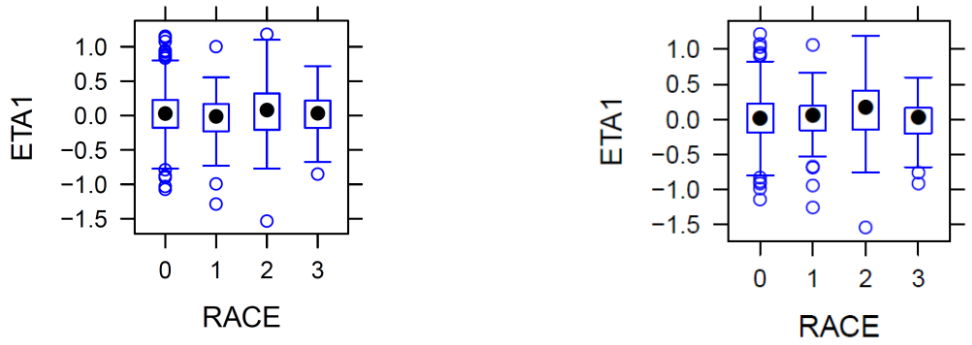


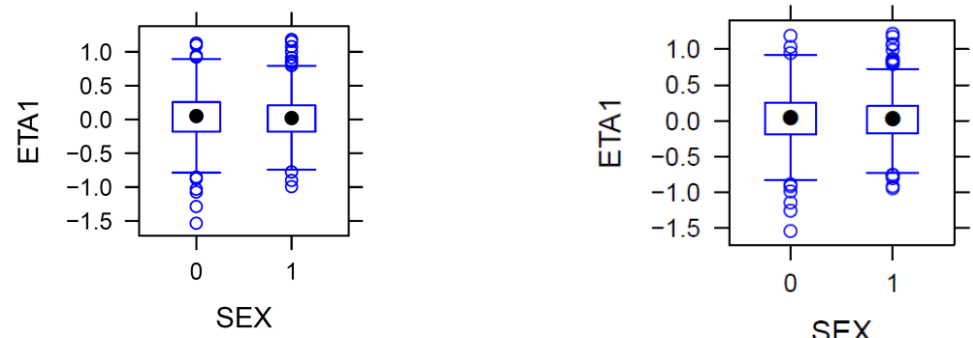
Figure 36. Eta (CL) versus Covariates for applicant's final model (run1.mod) and Reviewer's full covariate model (run28.mod)



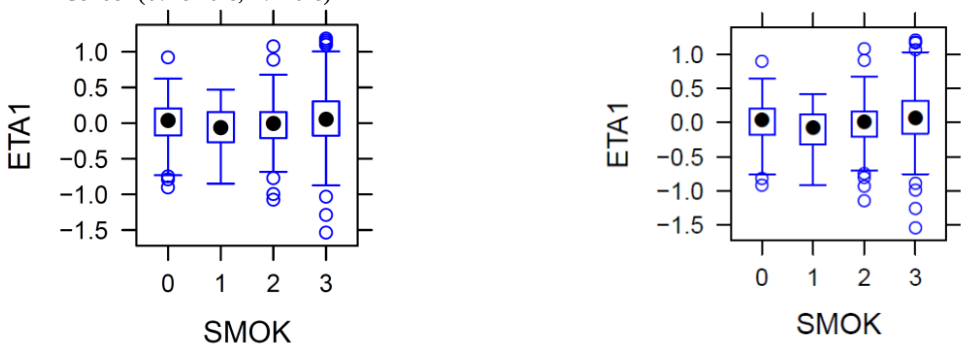
Time-dependent CYP1A2 activity (-2: strong inhibitor, -1: moderate inhibitor, 0: no effect, 1: moderate inducer). Not detectable in ETA plots



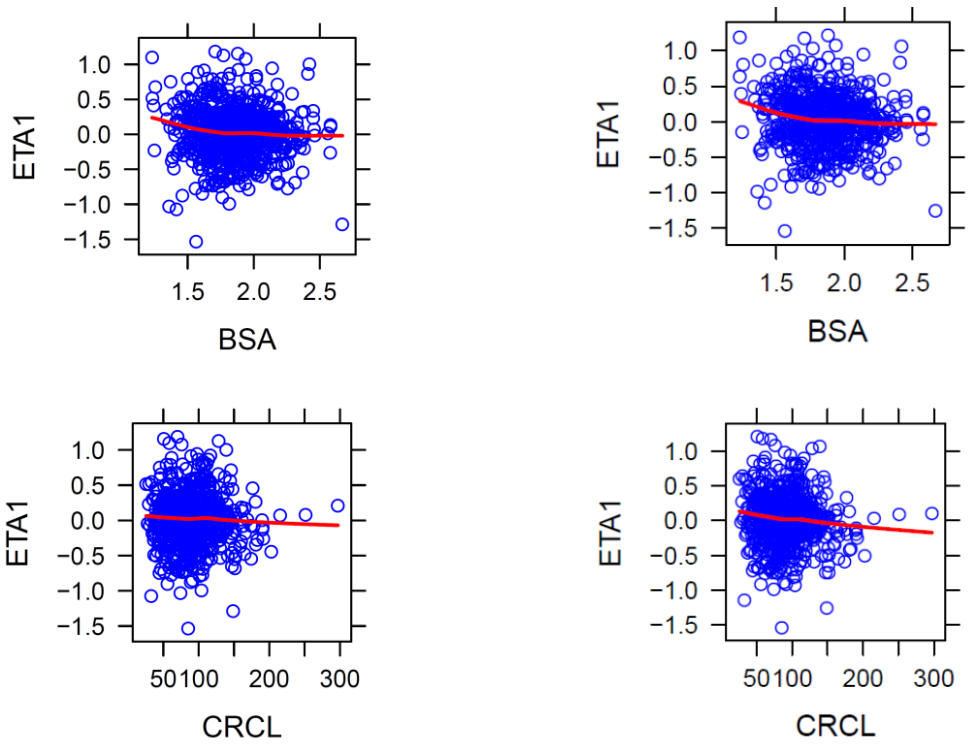
Race (0: white, 1: black, 2: Asian, 3: other)



Gender (0: female, 1: male)



Smoker status (0: never, 1: current, 2: former, 3: unknown)



Comment: *There appears not to be much improvement in ETA plots following the inclusion of covariates.*

Table 40. Covariates correlation

	CYP1A2 inh	Sex	Race	CrCL	BSA	Bilirubin	Age	AST	Smoking
CYP1A2 inh	1								
Sex	0	1							
Race	0.03	-0.03	1						
CrCL	0	-0.05	-0.02	1					
BSA	0	**0.46**	**-0.3**	**0.38**	1				
Bilirubin	0	0.09	0.08	0.04	0.05	1			
Age	0.02	0	-0.12	**-0.56**	-0.09	-0.05	1		
AST	-0.02	0.03	0	0.12	0.12	0.11	-0.07	1	
Smoking	-0.01	0.08	0.14	0.06	0.07	0.19	-0.15	0.03	1

Comment: *BSA and Age was excluded from covariate modeling due to significant correlation with other covariates.*

4 LISTING OF ANALYSES CODES AND OUTPUT FILES

(b) (4)

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