Model-Informed Drug Development (MIDD) for Ixazomib, an Oral Proteasome Inhibitor

Neeraj Gupta,¹ Michael J. Hanley,¹ Paul M. Diderichsen,² Huyuan Yang,¹
Yeamin Huh,³ Alice Ke,⁴ Zhaoyang Teng,¹ Richard Labotka,¹
Deborah Berg,¹ Chirag Patel,¹ Guohui Liu,¹ Helgi van de Velde,¹
and Karthik Venkatakrishnan¹

¹Millennium Pharmaceuticals Inc., Cambridge, MA, USA,
a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
²Certara Strategic Consulting, Breda, The Netherlands
³Ann Arbor Pharmacometrics Group, Ann Arbor, MI, USA
⁴Certara USA, Inc., Princeton, NJ, USA
Ixazomib, an oral proteasome inhibitor

- Ixazomib in combination with lenalidomide and dexamethasone (Rd) is approved for the treatment of previously treated multiple myeloma (MM) in 40 countries.

- Approval was based on the results of the global, randomized, double-blind, placebo-controlled, phase 3 TOURMALINE-MM1 study in relapsed/refractory MM (RRMM).\(^1\)

MIDD across the development continuum for ixazomib

BSA, body surface area; Conc, concentration; MBMA, model-based meta-analysis; MIDD, model-informed drug development; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; PTS, probability of technical success; RRMM, relapsed/refractory multiple myeloma
Switch from BSA-based to fixed dosing  
(N=137 patients)

- No effect of BSA on clearance based on population PK analysis using data from four phase 1 studies

- Clinical development switched posology from BSA-based to fixed dosing, simplifying capsule strength manufacture and dosing in global clinical studies

BSA, body surface area; PK, pharmacokinetics

Concentration-QTc analysis in lieu of a dedicated QTc study (N=245 patients)

- Ixazomib did not prolong the QTc interval at clinically relevant exposures
  - At the 4 mg dose, mean change from baseline in QTcF was estimated to be 0.07 msec (90% CI: −0.22, 0.36) from the model-based analysis

- From USPI: NINLARO did not prolong the QTc interval at clinically relevant exposures based on pharmacokinetic–pharmacodynamic analysis of data from 245 patients

USPI, United States Prescribing Information
Population PK analysis to examine effect of intrinsic and extrinsic factors on ixazomib PK (N=755 patients)

- No dose adjustment of ixazomib is required based on
  - BSA
  - Sex
  - Age
  - Race
  - Mild/moderate renal impairment,
  - Mild hepatic impairment

For BSA and Age, median values are compared 5th and 95th percentile

AUC, area under the curve; BSA, body surface area; HI, hepatic impairment; PK, pharmacokinetics; RI, renal impairment

Application of a PBPK model to facilitate regulatory review

- Ixazomib AUC not meaningfully altered with strong CYP3A inhibitors, indicating minor role for CYP3A in ixazomib clearance
  - However, strong CYP3A inducer rifampin decreased AUC by 74%

- Clinical DDI study results reconciled well by PBPK model incorporating minor contribution of CYP3A to overall ixazomib clearance
  - Model quantitatively considered the strength of induction of CYP3A and intestinal P-glycoprotein by rifampin

Results used during regulatory review to explain clinically significant effect of rifampin despite lack of strong CYP3A inhibitor effect

AUC, area under the curve; CYP, cytochrome P450; DDI, drug-drug interaction; PBPK, physiologically-based pharmacokinetic

TOURMALINE-MM1:
A randomized, double-blind phase III study of ixazomib + lenalidomide-dexamethasone (IRd) vs placebo-Rd in RRMM

Global, double-blind, randomized, placebo-controlled study design

**Ixazomib + Lenalidomide + Dexamethasone**
- Ixazomib: 4 mg on days 1, 8, and 15
- Lenalidomide: 25 mg* on days 1-21
- Dexamethasone: 40 mg on days 1, 8, 15, 22

**Placebo + Lenalidomide + Dexamethasone**
- Placebo: on days 1, 8, and 15
- Lenalidomide: 25 mg* on days 1-21
- Dexamethasone: 40 mg on days 1, 8, 15, 22

Repeat every 28 days until progression, or unacceptable toxicity

**Stratification:**
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

**Primary endpoint:**
- PFS

**Key secondary endpoints:**
- OS
- OS in patients with del(17p)

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*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

ISS, International Staging System; OS, overall survival; PFS, progression-free survival; PI, proteasome inhibitor

Ixazomib exposure was not a significant predictor of PFS ($p=0.25$)

- Median PFS was longer in all ixazomib exposure quartiles in the ixazomib-Rd arm compared to the placebo-Rd arm of the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n/N (%)</th>
<th>Median PFS, months</th>
<th>HR (95% CI) vs placebo-Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRd 1st quartile</td>
<td>32/86 (37)</td>
<td>20.6</td>
<td>0.675 (0.461–0.989)</td>
</tr>
<tr>
<td>IRd 2nd quartile</td>
<td>29/85 (34)</td>
<td>21.4</td>
<td>0.646 (0.434–0.961)</td>
</tr>
<tr>
<td>IRd 3rd quartile</td>
<td>30/86 (35)</td>
<td>16.8</td>
<td>0.748 (0.506–1.105)</td>
</tr>
<tr>
<td>IRd 4th quartile</td>
<td>31/85 (36)</td>
<td>18.4</td>
<td>0.794 (0.540–1.167)</td>
</tr>
<tr>
<td>Placebo-Rd</td>
<td>157/362 (43)</td>
<td>14.7</td>
<td>--</td>
</tr>
</tbody>
</table>

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Exposure–safety analyses from TOURMALINE-MM1: relationship between ixazomib exposure and TEAEs

Statistically significant relationships were identified between ixazomib exposure and the probability of TEAEs of clinical interest, supporting dose reduction guidelines.

Exposure–response analyses to support the dose-titration approach in phase 3 ixazomib maintenance studies

- At a 3 mg dose of ixazomib, the analysis predicted that the probabilities of TEAEs would be reduced compared to the 4 mg dose.

- Accordingly, to appropriately balance benefit vs risk, a starting dose of 3 mg with escalation to 4 mg, if tolerated, is being used in the phase 3 maintenance trials.

**TOURMALINE-MM3 (NCT02181413):**
Phase 3 study of ixazomib vs placebo as maintenance therapy post-ASCT in multiple myeloma patients with post-transplant response (≥PR)

**TOURMALINE-MM4 (NCT02312258):**
Phase 3 study of ixazomib vs placebo as maintenance therapy in multiple myeloma patients not eligible for ASCT achieving ≥PR after 6–12 months of initial therapy

ASCT, autologous stem cell transplantation; NDMM, newly diagnosed multiple myeloma; TEAE, treatment-emergent adverse event

Model-based meta-analysis (MBMA) for Go/No-Go decision making

- MBMA predicted a PFS of 20 months based on an ORR of 78% for ixazomib-Rd, consistent with the reported results of TOURMALINE-MM1.

- This can help estimate the PTS to achieve gold-standard efficacy targets in the target product profile, informing ‘GO/No-GO’ decisions at the molecule, as well as cross-molecule/portfolio level when comparing assets being developed for a common indication.

\[ \text{Model: } PFS = -23.46 + 0.56 \times \text{ORR} \]

Cl, confidence interval; ICd, ixazomib, cyclophosphamide, dexamethasone; ORR, overall response rate; PFS, progression-free survival; PTS, probability of technical success; TPP, target product profile

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- Investigators
- Ixazomib team members

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Exposure–response analyses from TOURMALINE-MM1: relationship between ixazomib exposure and lenalidomide RDI

- Consistent with the findings of a phase 1/2 study of ixazomib-Rd, higher ixazomib exposures were associated with a lower probability of lenalidomide RDI ≥60% in TOURMALINE-MM1.

Exposure–response analyses from TOURMALINE-MM1: relationship between ixazomib exposure and lenalidomide RDI

- Exposure–response analysis results suggest that ixazomib doses higher than 4 mg, in combination with Rd, may lead to higher rates of TEAEs, and may negatively impact lenalidomide RDI
  - This may counteract the potential positive effects of a higher ixazomib dose on the overall efficacy of ixazomib-Rd

- This analysis supported the dose-reduction guidelines in the Japan phase 2 bridging study to maximize the benefit–risk profile for this population

RDI, relative dose intensity; TEAE, treatment-emergent adverse event