The Journal of Clinical Pharmacology
2017, 0(0) 1–8

DOI: 10.1002/jcph.987

A Phase 1 Study to Assess the Relative Bioavailability of Two Capsule Formulations of Ixazomib, an Oral Proteasome Inhibitor, in Patients With Advanced Solid Tumors or Lymphoma

Michael J. Hanley, PharmD, PhD[1], Neeraj Gupta, PhD, FCP[1], Karthik Venkatakrishnan, PhD, FCP[1], Alberto Bessudo, MD[2], Sunil Sharma, MD[3], Bert H. O'Neil, MD[4], Bingxia Wang, PhD[1], Helgi van de Velde, MD, PhD[1], and John Nemunaitis, MD[5]

Abstract

The oral proteasome inhibitor ixazomib is approved in multiple countries in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. Two oral capsule formulations of ixazomib have been used during clinical development. This randomized, 2-period, 2-sequence crossover study (Clinicaltrials.gov identifier NCT01454076) assessed the relative bioavailability of capsule B in reference to capsule A in adult patients with advanced solid tumors or lymphoma. The study was conducted in 2 parts. In cycle 1 (pharmacokinetic cycle), patients received a 4-mg dose of ixazomib as capsule A or capsule B on day 1, followed by a 4-mg dose of the alternate capsule formulation on day 15. Pharmacokinetic samples were collected over 216 hours postdose. After the pharmacokinetic cycle, patients could continue in the study and receive ixazomib (capsule B only) on days 1, 8, and 15 of each 28-day cycle. Twenty patients were enrolled; of these, 14 were included in the pharmacokinetic-evaluable population. Systemic exposures of ixazomib were similar after administration of capsule A or capsule B. The geometric least-squares mean ratios (capsule B versus capsule A) were 1.16 for C_{max} (90% confidence interval [CI], 0.84–1.61) and 1.04 for AUC_{0-216} (90%CI, 0.91–1.18). The most frequently reported grade 3 drug-related adverse events were fatigue (15%) and nausea (10%); there were no grade 4 drug-related adverse events. These results support the combined analysis of data from studies that used either formulation of ixazomib during development.

Keywords

multiple myeloma, ixazomib, bioavailability, pharmacokinetics

Proteasome inhibitors are a key backbone of therapy for multiple myeloma (MM),[1] and the proteasome inhibitor bortezomib is also approved for the treatment of mantle cell lymphoma.[2] Bortezomib and another currently approved proteasome inhibitor, carfilzomib, are administered via intravenous or subcutaneous injection.[3] In contrast, ixazomib is the first oral proteasome inhibitor to be investigated clinically[4] and, as of March 2017, is approved in the United States, the European Union, Canada, Australia, Israel, Singapore, and Switzerland, in combination with lenalidomide and dexamethasone, for the treatment of patients with MM who have received at least 1 prior therapy,[5] based on data from the TOURMALINE-MM1 trial.[6] Ixazomib is also under phase 3 investigation in newly diagnosed MM (NCT01850524), in the maintenance setting in MM (NCT02181413 and NCT02312258), and in primary systemic light-chain (AL) amyloidosis (NCT01659658). In the preclinical setting, ixazomib exhibited antiproliferative activity in tumor cell lines, with potent antitumor activity observed in xenograft models of MM, lymphoma, and some solid tumors.[7–9]

Ixazomib is administered as a stable citrate ester, designated as ixazomib citrate. Under physiological

[1]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
[2]California Cancer Associates for Research and Excellence, San Diego, CA, USA
[3]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA
[4]Indiana University Simon Cancer Center, Indianapolis, IN, USA
[5]Mary Crowley Cancer Research Center, Dallas, TX, USA

Submitted for publication 21 April 2017; accepted 22 June 2017.

Corresponding Author:
Michael J. Hanley, PharmD, PhD, Quantitative Clinical Pharmacology, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, 40 Landsdowne Street, Cambridge, MA 02139
Email: Michael.Hanley@takeda.com

conditions, ixazomib citrate rapidly hydrolyzes to the biologically active boronic acid ixazomib, which potently, reversibly, and selectively inhibits the 20S proteasome.[7–9] After oral administration, ixazomib is rapidly absorbed[10,11] and exhibits dose- and time-independent pharmacokinetics (PK).[12,13] The PK of ixazomib is unaffected by age, body surface area, mild hepatic impairment, or mild to moderate renal impairment based on population PK analysis.[12,13] In a phase 1 food-effect study, administration of ixazomib after consumption of a high-calorie, high-fat meal decreased both the rate and extent of ixazomib absorption. Accordingly, ixazomib should be administered on an empty stomach, at least 1 hour before or at least 2 hours after food.[14] In addition, systemic exposures of ixazomib were increased in patients with severe renal impairment (creatinine clearance < 30 mL/minute) or end-stage renal disease requiring dialysis[15] and in patients with moderate or severe hepatic impairment.[16] Therefore, a reduced starting dose of ixazomib is recommended in these special patient populations.

The drug substance is formulated as immediate-release capsules, and 2 oral capsule formulations of ixazomib have been used during its clinical development. The capsule A formulation, which was used in the first 2 phase 1 single-agent studies of ixazomib in patients with relapsed/refractory MM,[10,11] consisted of the drug substance and microcrystalline cellulose. The capsule B formulation, which is the commercially available formulation, consists of the drug substance, microcrystalline cellulose, talc, and magnesium stearate. The capsule B formulation has been used in all other oral ixazomib studies to date,[17–20] including the pivotal TOURMALINE-MM1 trial,[6] and is being used in the ongoing phase 3 trials in MM[21,22] and AL amyloidosis.[23]

During clinical development, data collected from patients receiving the capsule A formulation or the capsule B formulation were used to conduct several integrated PK, PK/pharmacodynamic, and safety analyses. These analyses included a pooled population PK analysis that supported switching from body surface area–based dosing to fixed dosing in early development,[12] a concentration-QTc analysis using data from 4 phase 1 studies,[24] an exposure–safety/efficacy analysis that informed the selection of the ixazomib dose being studied in the maintenance setting for MM,[25] a pooled population PK analysis of phase 1–3 clinical study data,[13] and integrated analyses of clinical safety.[26] Thus, this phase 1 relative bioavailability study was performed to compare the PK of ixazomib after administration of the capsule A or capsule B formulation to bridge the available data from clinical trials conducted with either formulation during development.

Methods

Patients

The study protocol and protocol amendments were approved by the institutional review board (Alpha Institutional Review Board, University of Utah Institutional Review Board, Indiana University Institutional Review Board, and Mary Crowley Research Center Institutional Review Board) at each participating center. The trial was conducted according to the stipulations set out in the Declaration of Helsinki and International Conference on Harmonisation Guideline for Good Clinical Practice. The study was registered at www.clinicaltrials.gov as NCT01454076. All patients provided written informed consent.

Adult patients with histologically or cytologically confirmed metastatic and/or advanced solid tumor malignancies or lymphoma, for which no effective standard treatment was available, were eligible to enroll in the study. For patients with advanced solid tumors, radiographically measurable disease was defined per Response Evaluation Criteria in Solid Tumors, version 1.1.[27] For patients with lymphoma, radiographically or clinically measurable disease was defined as at least 1 measurable tumor mass > 1.5 cm in the long axis and > 1.0 cm in the short axis that had not been previously irradiated or grown since previous irradiation as defined by International Working Group criteria.[28]

Additional criteria for participation included an Eastern Cooperative Oncology Group performance status of 0 or 1, an absolute neutrophil count (ANC) $\geq 1.25 \times 10^9$/L, and a platelet count $> 100 \times 10^9$/L ($\text{ANC} \geq 1.0 \times 10^9$/L and platelet count $> 75 \times 10^9$/L for patients with lymphoma and underlying malignant bone marrow involvement), total bilirubin < 1.5 times the upper limit of the normal range (ULN), alanine transaminase or aspartate transaminase ≤ 2.5 times the ULN, and a calculated creatinine clearance > 60 mL/min. Patients also had to have recovered from the reversible effects of prior anticancer therapy.

Patients with grade > 2 peripheral neuropathy or any comorbid systemic illness or other severe concurrent disease that, in the judgment of the investigator, would have made the patient inappropriate for entry into the study or interfered significantly with the assessment of safety and/or toxicity were not eligible to participate in the study. Patients who received systemic treatment with strong inhibitors of CYP1A2 or CYP3A or strong CYP3A inducers within 14 days before the first dose of ixazomib were also not eligible. In addition, use of moderate CYP1A2 or CYP3A inhibitors was prohibited during cycle 1 (the PK cycle) of the study. Patients were also excluded if they had symptomatic brain metastases or if they had received radiotherapy

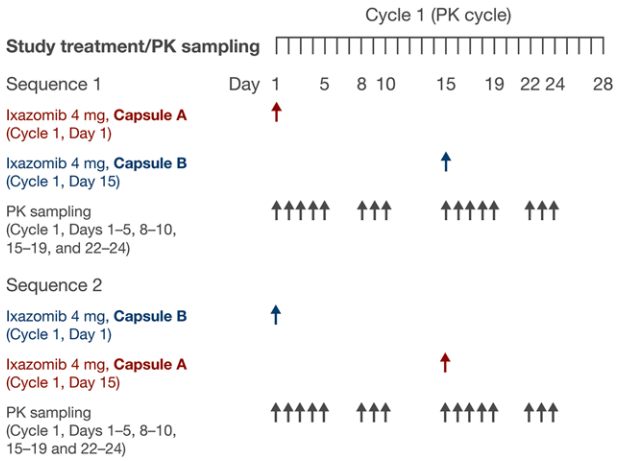

Figure 1. Study design — study treatment and PK sampling during the PK cycle. Arrows indicate dosing or PK sampling days during cycle 1. Blood samples were collected at the following times after the administration of ixazomib on days 1 and 15: predose and 0.5, 1, 1.5, 2, 3, 4, 8, 24, 48, 72, 96, 168, 192, and 216 hours postdose. After cycle 1, patients received ixazomib at a starting dose of 4 mg on days 1, 8, and 15 of each 28-day cycle.

within 21 days, major surgery within 14 days, prior rituximab or other unconjugated antibody treatment within 42 days, any investigational products or systemic antineoplastic therapies within 21 days, autologous stem cell transplantation within 6 months, or allogeneic stem cell transplantation at any time before the first dose of ixazomib.

Study Design

The study was conducted in 2 parts. In cycle 1, which was the PK cycle, a randomized, 2-period, 2-sequence crossover study design was used (Figure 1). On day 1 of the PK cycle (cycle 1), patients received a 4-mg oral dose of ixazomib as the capsule A or capsule B formulation, followed by a 4-mg oral dose of the alternate capsule formulation (ie, capsule B or capsule A) on day 15. After completion of the PK cycle (ie, cycle 2 and beyond), patients could continue in the study and receive ixazomib, as the capsule B formulation only, on days 1, 8, and 15 of each 28-day cycle. The starting ixazomib dose for cycle 2 was 4 mg, with the option of dose escalation to 5.3 mg in cycle 4 and beyond. All ixazomib doses were administered on an empty stomach, with patients fasting from food and fluids, except for water and prescribed medications for 2 hours before and 1 hour after each dose. After the PK cycle, dose adjustments, interruptions, and/or delays were allowed based on clinical and laboratory findings, as per prespecified dose modification guidelines.

The primary objective of the study was to estimate the relative bioavailability of ixazomib in the capsule B formulation in reference to the capsule A formulation. An additional objective was to characterize the safety and tolerability of oral ixazomib in patients with advanced solid tumors or lymphoma. The primary end point of the study was the ratio of geometric mean maximum observed plasma concentration (C_{max}) and the area under the plasma ixazomib concentration–time curve from time zero to 216 hours postdose ($AUC_{0–216}$) of capsule B versus capsule A and the corresponding 90% confidence intervals (CIs).

Assessments

Blood samples for the measurement of plasma ixazomib concentrations were collected at the following prespecified times during cycle 1 after ixazomib administration on day 1 and day 15: predose and 0.5, 1, 1.5, 2, 3, 4, 8, 24, 48, 72, 96, 168, 192, and 216 hours postdose. Plasma ixazomib concentrations were measured using a previously described validated liquid chromatography–tandem mass spectrometry assay with a dynamic range of 0.5–500 ng/mL.[14,16]

Adverse events (AEs) were evaluated throughout the study and up to 30 days after the last dose of ixazomib or the start of subsequent antineoplastic therapy. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analyses

All patients who received at least 1 dose of ixazomib were included in the safety population. The PK-evaluable population was defined as all patients who received the protocol-specified doses of ixazomib during cycle 1 without dose reductions or interruptions, did not receive any excluded concomitant medication through the completion of PK sampling, and had sufficient concentration–time data to permit the calculation of PK parameters by noncompartmental analysis methods. Patients who were not PK-evaluable were replaced.

The sample size calculation was based on the expected 2-sided 90%CI for the difference in the paired log-transformed AUC means on day 1 and day 15. On the basis of PK data from a previously reported study,[11] the within-patient coefficient of variation was estimated to be 32%. Assuming the AUC ratio for capsule B versus capsule A was 1, with a sample size of 14 PK-evaluable patients, the 90%CI for the AUC ratio was expected to be 0.811 to 1.234.

Plasma PK parameters for ixazomib were calculated using noncompartmental analysis methods with Phoenix WinNonlin, version 6.2 (Pharsight, St. Louis, Missouri). PK parameters were summarized using descriptive statistics. For the relative bioavailability estimation, geometric mean ratios for C_{max} and $AUC_{0–216}$ for capsule B versus capsule A and the corresponding 2-sided 90%CIs were calculated using a

Table 1. Patient Baseline Demographics and Disease Characteristics

	Safety Population (n = 20)
Age (years), median (range)	64 (29–76)
Male, n (%)	9 (45)
Race, n (%)[a]	
White	15 (75)
African American	2 (10)
Asian	0
Other/not reported	3 (15)
Body weight (kg), median (range)	68.1 (46.9–93.5)
Disease type, n (%)	
Colorectal[b]	6 (30)
Ovarian	3 (15)
Pancreatic	2 (10)
Endometrial	1 (5)
Esophageal	1 (5)
Non–small cell lung cancer	1 (5)
Other[c]	6 (30)
Disease stage, n (%)	
IV	19 (95)
IVB	1 (5)
ECOG performance status, n (%)	
0	5 (25)
1	15 (75)
Time since initial diagnosis (months), median (range)	41 (4–108)
Prior antineoplastic therapy, n (%)	20 (100)
Prior radiation therapy, n (%)	13 (65)
Prior surgical procedure, n (%)	19 (95)

ECOG, Eastern Cooperative Oncology Group.

[a]Not reported for 2 patients.

[b]Includes 4 patients with colon cancer and 2 patients with colorectal cancer.

[c]Other tumor types included adenocystic carcinoma, breast, kidney, melanoma, perineural, and sarcoma.

mixed-effects analysis of variance (ANOVA) model, fitting terms for treatment (capsule A or capsule B), sequence, and period as fixed effects. Patient within sequence was treated as a random effect in the model. After log-transformation, C_{max} and $AUC_{0–216}$ were analyzed separately. Point estimates (least-squares means) and adjusted 90%CIs for the difference of least-squares means between treatments (capsule A or capsule B) were calculated and then exponentially back-transformed to provide point and CI estimates for the ratios of interest.

Results

Patients and Treatment Exposure

Twenty patients were enrolled in the study. Baseline patient and disease characteristics are shown in Table 1. The most common cancer types were colorectal cancer in 6 patients (30%), ovarian cancer in 3 patients (15%), and pancreatic cancer in 2 patients (10%). Patients received a median of 2 cycles of ixazomib (range, 1–7), with 5 patients (25%) receiving ≥4 cycles of treatment and 2 patients (10%; 1 patient with colorectal cancer and 1 patient with adenocystic carcinoma) receiving ≥6 cycles of treatment. The reason for study discontinuation was disease progression in 15 patients (75%), patient withdrawal in 3 patients (15%), and AEs in 2 patients (10%).

All patients received concomitant medications during the study. The most frequently reported concomitant medications were opioids in 17 patients (85%), antiemetics and antinauseants in 10 patients (50%), and laxatives in 10 patients (50%). Three patients (15%) received warfarin, in 2 patients for a medical history of deep vein thrombosis and in 1 patient as prophylaxis of port patency. Six patients (30%) received antihistamines for systemic use, including 2 patients for medical history and 4 patients for treatment of AEs. Five patients (25%) received direct-acting antivirals, including 3 patients who received acyclovir (2 for AEs and 1 for a medical history of chemotherapy rash), 1 patient who received valacyclovir for herpes prophylaxis, and 1 patient who received famciclovir for an AE. Five patients (25%) received gabapentin, including 3 patients for a medical history of neuropathy, 1 patient for neuropathic pain, and 1 patient for neck pain. Six patients (30%) received red blood cell transfusions.

Pharmacokinetics

Fourteen patients were included in the PK-evaluable population. Seven patients received the capsule A formulation on day 1 and the capsule B formulation on day 15 of the PK cycle, and 7 patients received the capsule B formulation on day 1 and the capsule A formulation on day 15. Figure 2 shows the mean plasma ixazomib concentration–time profiles after administration of capsule A or capsule B.

Ixazomib was rapidly absorbed after administration of either capsule formulation, with a median T_{max} of approximately 1.3 hours for both formulations (Table 2). The geometric mean values for C_{max} and $AUC_{0–216}$ were also similar after administration of capsule A or capsule B. The geometric least-squares mean ratio (90%CI) for capsule B versus capsule A was 1.16 (0.84–1.61) for C_{max} and 1.04 (0.91–1.18) for $AUC_{0–216.}$ A statistically significant period effect was observed in the ANOVA for $AUC_{0–216}$, indicating higher exposures in period 2 versus period 1 (ratio of period 2 $AUC_{0–216}$ to period 1 $AUC_{0–216}$ estimated as 1.63). However, this period effect was accounted for during estimation of the geometric least-squares mean ratio and the 90% confidence interval.

Of note, a period effect of comparable magnitude (2.21-fold) has also been recently reported in another 2-period crossover study that was designed to evaluate the effect of food on ixazomib PK.[14] Although the reasons for the observed period effect are not entirely clear, it may be explained in part by the long terminal half-life of ixazomib (approximately 9.5 days), leading to some

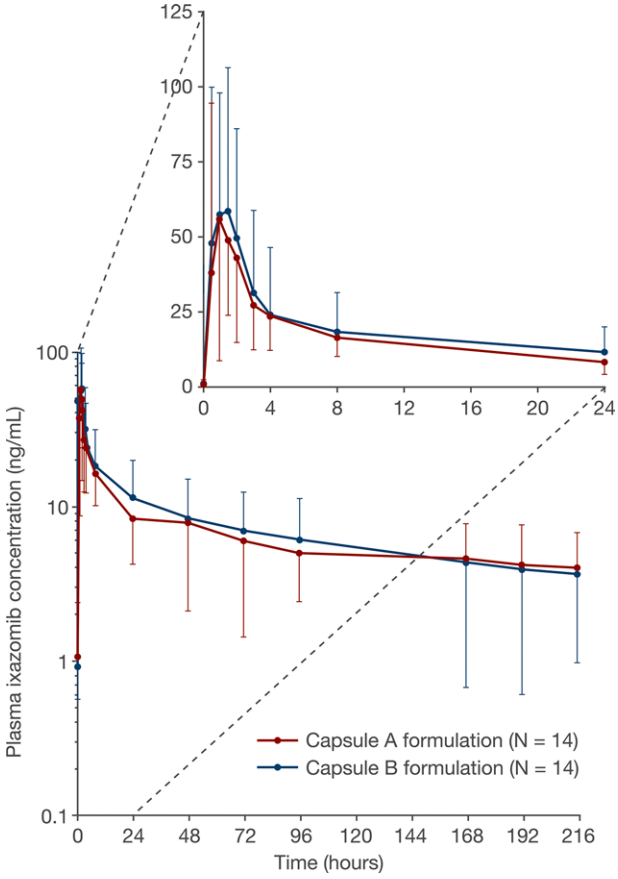

Figure 2. Mean ± SD plasma ixazomib concentration–time profiles after administration of the capsule A or capsule B formulation (n = 14). The inset shows the mean plasma ixazomib concentrations over the first 24 hours after dosing. SD, standard deviation.

level of accumulation in period 2 despite the 14-day washout period used in this study. A longer washout period would not have been practically feasible in this study in cancer patients; nevertheless, the crossover design with a balanced number of patients per sequence allowed an accurate and precise estimation of the relative bioavailability of capsule B versus capsule A after statistically accounting for the underlying period effect.

Safety

All 20 patients enrolled in the study were included in the safety population. All patients reported at least 1 treatment-emergent AE, and 17 patients (85%) had at least 1 drug-related AE (Table 3). The most common drug-related AEs regardless of grade included nausea (50%), fatigue (35%), diarrhea (35%), vomiting (30%), and decreased appetite (20%); see Table 4. Drug-related grade 3 AEs were reported in 6 patients (30%). The most frequently reported drug-related grade 3 AEs were fatigue (15%) and nausea (10%). No drug-related grade 4 AEs were reported during the study. Three patients (15%) experienced at least 1 AE resulting in discontinuation of ixazomib; 1 patient experienced aspartate aminotransferase increase and blood alkaline phosphatase increase, 1 patient experienced macular rash and stomatitis, and 1 patient experienced decreased appetite, pyrexia, acute febrile neutrophilic dermatosis, dehydration, pancytopenia, pleural effusion, and blood albumin decrease.

Table 2. Plasma PK Parameters of Ixazomib After Administration of Capsule A or Capsule B

Parameter	Ixazomib Capsule A (Reference), n = 14	Ixazomib Capsule B (Test), n = 14	Capsule B Versus Capsule A, Geometric Least-Squares Mean Ratio (90%CI), Test/Reference
T_{max} (h), median (range)	1.29 (0.52–3.0)	1.25 (0.50–7.5)	—
C_{max} (ng/mL), geometric mean (%CV)	61.9 (64)	71.9 (52)	1.16 (0.84–1.61)
$AUC_{0–216}$ (ng·h/mL), geometric mean (%CV)	1280 (62)	1330 (77)	1.04 (0.91–1.18)

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

Table 3. Summary of Treatment-Emergent Adverse Events and On-Study Deaths

	Safety Population (n = 20)
AEs, n (%)	
Any AE	20 (100)
Any drug-related AE	17 (85)
Any grade ≥ 3 AE	11 (55)
Any drug-related grade ≥ 3 AE	6 (30)
Any serious AE	5 (25)
Any drug-related serious AE	1 (5)
AE leading to discontinuation of ixazomib	3 (15)
On-study deaths, n (%)	1 (5)

AE, adverse event.

Discussion

This study was conducted to assess the relative bioavailability of the 2 oral capsule formulations of ixazomib that were administered during the clinical development program. The findings showed that systemic exposures of ixazomib were similar after administration of the capsule A formulation, which was the formulation used in 2 phase 1 studies of oral ixazomib in patients with relapsed/refractory MM,[10,11] and the capsule B formulation, which has been used in all other studies and is available commercially.

The geometric least-squares mean ratio (capsule B versus capsule A) for $AUC_{0–216}$ was 1.04, with a

Table 4. Summary of the Most Common Any-Grade (≥5% of Patients) and All Grade ≥ 3 (≥1 Patient) Drug-Related AEs

Any-Grade Drug-Related AEs, n (%)	Safety Population (n = 20)
Nausea	10 (50)
Diarrhea	7 (35)
Fatigue	7 (35)
Vomiting	6 (30)
Decreased appetite	4 (20)
Asthenia	3 (15)
Dehydration	3 (15)
Pyrexia	3 (15)
Chills	2 (10)
Constipation	2 (10)
Pruritus	2 (10)
Thrombocytopenia	2 (10)
Weight decreased	2 (10)
Maculopapular rash	1 (5)
Grade ≥ 3 drug-related AEs, n (%)	
Fatigue	3 (15)
Nausea	2 (10)
Acute febrile neutrophilic dermatosis	1 (5)
Leukopenia	1 (5)
Neutropenia	1 (5)
Pancytopenia	1 (5)
Thrombocytopenia	1 (5)
Vomiting	1 (5)

AE, adverse event.

90%CI of 0.91 to 1.18, which is within the accepted range of 80% to 125% for establishing bioequivalence in clinical PK studies.[29,30] The corresponding ratio for C_{max} was 1.16, with a 90%CI of 0.84 to 1.61. Although the upper bound of the 90%CI for C_{max} exceeded 125%, the difference in the observed C_{max} values between formulations in this study is unlikely to be clinically meaningful. For example, after once-weekly intravenous bolus administration of ixazomib at the maximum tolerated dose of 2.34 mg/m^2, the geometric mean C_{max} achieved following repeat-dose administration (803 ng/mL)[31] substantially exceeds the geometric mean C_{max} values observed in the present study following administration of the approved 4-mg oral dose of ixazomib (61.9–71.9 ng/mL). Furthermore, ixazomib did not produce clinically relevant changes in electrocardiogram parameters (eg, heart rate, QTc) over a wide range of concentrations (with 26% of the concentrations contributing to the QTc analysis being greater than the mean C_{max} for the approved 4-mg dose),[24] and the principal AEs observed following oral dose administration of ixazomib (eg, nausea, vomiting, diarrhea, rash, thrombocytopenia) are expected to be related to total systemic exposure, as indicated by exposure–safety analyses of clinical data.[25,32]

The capsule A formulation was used in a phase 1 study that enrolled patients with MM and administered ixazomib as a single agent.[10] In this study, the single-agent maximum tolerated dose for the once-weekly dosing regimen was 2.97 mg/m^2. Subsequently, a phase 1/2 study was conducted that examined the capsule B formulation in combination with lenalidomide and dexamethasone for the treatment of patients with MM.[17] The once-weekly maximum tolerated dose for ixazomib in this combination study was also 2.97 mg/m^2. The consistent maximum tolerated dose for once-weekly ixazomib in these studies, despite the administration of the capsule B formulation in combination with lenalidomide and dexamethasone, further indicates that the slightly higher C_{max} observed with the capsule B formulation in this relative bioavailability study is not clinically meaningful. Accordingly, the results of this relative bioavailability study supported the utilization of data collected in studies that administered either formulation of ixazomib for several PK/pharmacodynamic and integrated safety analyses that were conducted during development. These included a pooled population PK analysis that supported switching from body surface area–based dosing to fixed dosing in early development,[12] a concentration–QTc analysis,[24] an exposure–safety/efficacy analysis that informed dose selection for ixazomib in the maintenance setting for MM,[25] a pooled population PK analysis of phase 1–3 clinical study data,[13] and integrated analyses of clinical safety.[26]

The reported AEs in this study were consistent with the known safety profile of ixazomib observed in previous studies in patients with MM, AL amyloidosis, lymphoma, and advanced solid tumors.[6,10,11,17,18,31,33,34] Common AEs included gastrointestinal events (ie, nausea, vomiting, and diarrhea) and fatigue. The majority of AEs were low grade. In fact, the only drug-related AEs to be reported at grade 3 severity in more than 1 patient were fatigue and nausea. However, it should be noted that patients received ixazomib for a limited duration in this study, with only 2 patients receiving ≥6 cycles of treatment. Importantly, the AEs reported in the present study appeared to be manageable with dose modifications and/or supportive care.

Conclusions

In conclusion, the results of this study demonstrated that the PK of ixazomib is similar after administration of the capsule A or the capsule B formulation, thereby supporting the combined analysis of data from clinical trials conducted with either formulation.

Acknowledgments

Writing support during the development of the manuscript was provided by Steve Hill of FireKite, an Ashfield company, part of UDG Healthcare plc, which was funded by

Millennium Pharmaceuticals, Inc., and complied with Good Publication Practice 3 ethical guidelines (Battisti WP, et al. *Ann Intern Med* 2015;163:461–464).

This work has been presented at the following meetings: poster presented at the 2016 Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, San Diego, California, March 8–12, 2016.

Declaration of Conflicting Interests

Michael J. Hanley, Neeraj Gupta, Karthik Venkatakrishnan, Bingxia Wang, and Helgi van de Velde are employees of Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Bert O'Neil, Sunil Sharma, Alberto Bessudo, and John Nemunaitis have no conflicts of interest to declare.

Funding

This work was funded by Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

References

1. Anderson KC, Alsina M, Atanackovic D, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2016. *J Natl Compr Canc Netw*. 2016;14(4):389–400.
2. Cheah CY, Seymour JF, Wang ML. Mantle Cell Lymphoma. *J Clin Oncol*. 2016;34(11):1256–1269.
3. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol*. 2016;17(1):27–38.
4. Richardson PG, Moreau P, Laubach JP, et al. The investigational proteasome inhibitor ixazomib for the treatment of multiple myeloma. *Future Oncol*. 2015;11(8):1153–1168.
5. Shirley M. Ixazomib: first global approval. *Drugs*. 2016;76 (3):405–411.
6. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621–1634.
7. Chauhan D, Tian Z, Zhou B, et al. In vitro and in vivo selective antitumor activity of a novel orally bioavailable proteasome inhibitor MLN9708 against multiple myeloma cells. *Clin Cancer Res*. 2011;17(16):5311–5321.
8. Kupperman E, Lee EC, Cao Y, et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Res*. 2010;70(5):1970–1980.
9. Lee EC, Fitzgerald M, Bannerman B, et al. Antitumor activity of the investigational proteasome inhibitor MLN9708 in mouse models of B-cell and plasma cell malignancies. *Clin Cancer Res*. 2011;17(23):7313–7323.
10. Kumar SK, Bensinger WI, Zimmerman TM, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. *Blood*. 2014;124(7):1047–1055.
11. Richardson PG, Baz R, Wang M, et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. *Blood*. 2014;124(7):1038–1046.
12. Gupta N, Zhao Y, Hui AM, Esseltine DL, Venkatakrishnan K. Switching from body surface area-based to fixed dosing for the investigational proteasome inhibitor ixazomib: a population pharmacokinetic analysis. *Br J Clin Pharmacol*. 2014;79(5):789–800.
13. Gupta N, Diderichsen PM, Hanley MJ, et al. Population pharmacokinetic analysis of ixazomib, an oral proteasome inhibitor, including data from the phase III TOURMALINE-MM1 study to inform labelling [published online ahead of print 2017]. *Clin Pharmacokinet*.
14. Gupta N, Hanley MJ, Venkatakrishnan K, et al. The effect of a high-fat meal on the pharmacokinetics of ixazomib, an oral proteasome inhibitor, in patients with advanced solid tumors or lymphoma. *J Clin Pharmacol*. 2016;56(10):1288–1295.
15. Gupta N, Hanley MJ, Harvey RD, et al. A pharmacokinetics and safety phase 1/1b study of oral ixazomib in patients with multiple myeloma and severe renal impairment or end-stage renal disease requiring haemodialysis. *Br J Haematol*. 2016;174(5):748–759.
16. Gupta N, Hanley MJ, Venkatakrishnan K, et al. Pharmacokinetics of ixazomib, an oral proteasome inhibitor, in solid tumour patients with moderate or severe hepatic impairment. *Br J Clin Pharmacol*. 2016;82(3):728–738.
17. Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. *Lancet Oncol*. 2014;15(13):1503–1512.
18. Merlini G, Sanchorawala V, Zonder JA, et al. Long-term outcome of a phase 1 study of the investigational oral proteasome inhibitor (PI) ixazomib at the recommended phase 3 dose (RP3D) in patients (pts) with relapsed or refractory systemic light-chain (AL) amyloidosis (RRAL) [abstract]. *Blood*. 2014;124:3450.
19. Richardson PG, Hofmeister CC, Rosenbaum CA, et al. Twice-weekly oral MLN9708 (ixazomib citrate), an investigational proteasome inhibitor, in combination with lenalidomide (len) and dexamethasone (dex) in patients (pts) with newly diagnosed multiple myeloma (MM): final phase 1 results and phase 2 data [abstract]. *Blood*. 2013;122:535.
20. San Miguel J, Hajek R, Spicka I, et al. Oral MLN9708, an investigational proteasome inhibitor, in combination with melphalan and prednisone in patients with previously untreated multiple myeloma: a phase 1 study [abstract]. *Haematologica*. 2012;97:118–119.
21. Palumbo A, Morgan GJ, Rajkumar SV, et al. Two phase 3 studies of the oral proteasome inhibitor (PI) ixazomib for multiple myeloma (MM) in the maintenance setting: TOURMALINE-MM3, and -MM4 [abstract]. *J Clin Oncol*. 2016;34:TPS8068.
22. San Miguel J, Moreau P, Rajkumar V, et al. Four phase 3 studies of the oral proteasome inhibitor (PI) ixazomib for multiple myeloma in the newly-diagnosed, relapsed/refractory, and maintenance settings: TOURMALINE-MM1, -MM2, -MM3, and -MM4 [abstract]. *Clin Lymphoma Myeloma Leuk*. 2015;15:e174.
23. Merlini G, Dispenzieri A, Berg D, et al. Phase 3 study of the oral proteasome inhibitor ixazomib for relapsed/refractory AL amyloidosis: TOURMALINE-AL1 [abstract]. *Clin Lymphoma Myeloma Leuk*. 2015;15:e60–e61.
24. Gupta N, Huh Y, Hutmacher MM, et al. Integrated nonclinical and clinical risk assessment of the investigational proteasome inhibitor ixazomib on the QTc interval in cancer patients. *Cancer Chemother Pharmacol*. 2015;76(3):507–516.
25. Gupta N, Labotka R, Liu G, Hui AM, Venkatakrishnan K. Exposure-safety-efficacy analysis of single-agent ixazomib,

an oral proteasome inhibitor, in relapsed/refractory multiple myeloma: dose selection for a phase 3 maintenance study. *Invest New Drugs*. 2016;34(3):338–346.
26. US Food and Drug Administration Center for Drug Evaluation and Research (CDER). Medical Review 208462Orig1s000: Ninlaro (ixazomib) Clinical Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208462Orig1s000MedR.pdf. Accessed February 22, 2017.
27. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247.
28. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579–586.
29. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on the investigation of bioequivalence. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed July 29, 2016.
30. US Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry — Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm389370.pdf. Accessed July 29, 2016.
31. Assouline SE, Chang J, Cheson BD, et al. Phase 1 dose-escalation study of IV ixazomib, an investigational proteasome inhibitor, in patients with relapsed/refractory lymphoma. *Blood Cancer J*. 2014;4:e251.
32. US Food and Drug Administration Center for Drug Evaluation and Research (CDER). Clinical Pharmacology and Biopharmaceutics Review 208462Orig1s000: Ninlaro (ixazomib) Clinical Pharmacology NDA Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208462Orig1s000ClinPharmR.pdf. Accessed February 22, 2017.
33. Gupta N, Goh YT, Min CK, et al. Pharmacokinetics and safety of ixazomib plus lenalidomide-dexamethasone in Asian patients with relapsed/refractory myeloma: a phase 1 study. *J Hematol Oncol*. 2015;8:103.
34. Smith DC, Kalebic T, Infante JR, et al. Phase 1 study of ixazomib, an investigational proteasome inhibitor, in advanced non-hematologic malignancies. *Invest New Drugs*. 2015;33(3):652–663.