

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208462Orig1s000

MEDICAL REVIEW(S)

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208462
Priority or Standard	Priority
Submit Date(s)	July 10, 2015
Received Date(s)	July 10, 2015
PDUFA Goal Date	March 10, 2016
Division/Office	DHP/OHOP
Reviewer Name(s)	Alexandria Schwarsin, MD
Review Completion Date	November 12, 2015
Established Name	Ixazomib
Trade Name	Ninlaro®
Applicant	Millennium Pharmaceuticals, Inc
Formulation	Capsules: 4 mg, 3 mg, and 2.3 mg
Dosing Regimen	4 mg taken orally on Days 1, 8, and 15 of a 28 day cycle
Applicant Proposed Indication(s)/Population(s)	For the treatment of patients with multiple myeloma who have received at least one prior therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	In combination with lenalidomide and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Table of Contents

Glossary.....	9
1 Executive Summary	10
1.1. Product Introduction.....	10
1.2. Conclusions on the Substantial Evidence of Effectiveness	10
1.3. Benefit-Risk Assessment	10
2 Therapeutic Context	14
2.1. Analysis of Condition.....	14
2.2. Analysis of Current Treatment Options	14
3 Regulatory Background	16
3.1. U.S. Regulatory Actions and Marketing History.....	16
3.2. Summary of Pre-submission/Submission Regulatory Activity.....	16
3.3. Foreign Regulatory Actions and Marketing History.....	18
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	18
4.1. Office of Scientific Investigations (OSI)	18
4.2. Product Quality	18
4.3. Clinical Microbiology	18
4.4. Nonclinical Pharmacology/Toxicology	18
4.5. Clinical Pharmacology	19
4.5.1. Mechanism of Action	19
4.5.2. Pharmacodynamics.....	19
4.5.3. Pharmacokinetics.....	19
4.6. Devices and Companion Diagnostic Issues	19
4.7. Consumer Study Reviews.....	19
5 Sources of Clinical Data and Review Strategy	20
5.1. Table of Clinical Studies.....	20
5.2. Review Strategy.....	24
6 Review of Relevant Individual Trials Used to Support Efficacy	24

6.1.	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	24
6.1.1.	Study Design.....	24
6.1.2.	Study Results.....	33
7	Integrated Review of Effectiveness	45
7.1.	Assessment of Efficacy Across Trials	46
7.1.1.	Primary Endpoints.....	46
7.1.2.	Secondary and Other Endpoints.....	46
7.2.	Additional Efficacy Considerations.....	46
7.2.1.	Considerations on Benefit in the Postmarket Setting	46
7.3.	Integrated Assessment of Effectiveness	46
8	Review of Safety	46
8.1.	Safety Review Approach	46
8.2.	Review of the Safety Database	47
8.2.1.	Overall Exposure	47
8.2.2.	Relevant characteristics of the safety population:	48
8.2.3.	Adequacy of the safety database:	49
8.3.	Adequacy of Applicant’s Clinical Safety Assessments.....	49
8.3.1.	Issues Regarding Data Integrity and Submission Quality	49
8.3.2.	Categorization of Adverse Events.....	49
8.3.3.	Routine Clinical Tests	49
8.4.	Safety Results	50
8.4.1.	Deaths	50
8.4.2.	Serious Adverse Events.....	54
8.4.3.	Dropouts and/or Discontinuations Due to Adverse Effects	55
8.4.4.	Significant Adverse Events	59
8.4.5.	Treatment Emergent Adverse Events and Adverse Reactions	59
8.4.6.	Laboratory Findings	60
8.4.7.	Vital Signs	62
8.4.8.	Electrocardiograms (ECGs).....	62

8.4.9. QT	62
8.4.10. Immunogenicity	62
8.5. Analysis of Submission-Specific Safety Issues	62
8.5.1. Thrombocytopenia.....	62
8.5.2. Gastrointestinal.....	63
8.5.3. Cutaneous reactions	64
8.5.4. Peripheral Neuropathy	65
8.5.5. Cardiac toxicities	66
8.5.6. Pulmonary toxicity	67
8.5.7. Eye disorders.....	68
8.5.8. PRES	69
8.5.9. Hypotension	69
8.5.10. Hepatic disorders.....	70
8.6. Specific Safety Studies/Clinical Trials	70
8.7. Additional Safety Explorations	70
8.7.1. Human Carcinogenicity or Tumor Development	70
8.7.2. Human Reproduction and Pregnancy	71
8.7.3. Pediatrics and Assessment of Effects on Growth	71
8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	71
8.7.5. Subgroup Analysis.....	71
8.8. Safety in the Postmarket Setting.....	74
8.8.1. Safety Concerns Identified Through Post-market Experience.....	74
8.8.2. Expectations on Safety in the Postmarket Setting	74
8.9. Additional Safety Issues From Other Disciplines.....	74
8.10. Integrated Assessment of Safety	74
9 Advisory Committee Meeting and Other External Consultations.....	75
10 Labeling Recommendations	75
10.1. Prescribing Information	75
10.2. Patient Labeling	76
11 Risk Evaluation and Mitigation Strategies (REMS)	76

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

12	Post-marketing Requirements and Commitments.....	76
13	Appendices	76
13.1.	References	76
13.2.	Financial Disclosure	76

Table of Tables

Table 1 Approved therapy for multiple myeloma	14
Table 2 Interactions with FDA.....	16
Table 3 List of Clinical Trials	21
Table 4 Patient Disposition	34
Table 5 Major Protocol Deviations	35
Table 6 Demographics of ITT population.....	36
Table 7 Countries of ITT population	37
Table 8 Baseline characteristics of the ITT population	38
Table 9 Prior treatments of ITT population	39
Table 10 Overall Treatment Compliance (%).....	40
Table 11 Concomitant Medications for the Safety Population	41
Table 12 Reason for Censoring from IRC PFS assessment.....	42
Table 13 PFS results per IRC.....	43
Table 14 Duration of Response.....	44
Table 15 Hazard Ratio for PFS for subpopulations	45
Table 16 Subgroups evaluation of First Interim Analysis of PFS per IRC	45
Table 17 Exposure for each drug by treatment arm for safety population	47
Table 18 Total dose administered	48
Table 19 Safety Database for Ixazomib Development.....	48
Table 20 Duration of Exposure for Ixazomib Development	48
Table 21 Narratives for patients who died on ixazomib arm within 30 days of study treatment	50
Table 22 Death Narratives within 30 days of last dose for Placebo arm.....	52
Table 23 Serious Adverse Events	54
Table 24 TEAE which resulted in discontinuation from the trial in the safety population	55
Table 25 TEAE which led to discontinuation, reduction, holding or delaying ixazomib or placebo	56
Table 26 Lowest grade of thrombocytopenia which resulted in dose modification.....	57
Table 27 Dose adjustment secondary to rash	58
Table 28 Dose Reductions secondary to neutropenia	58
Table 29 TEAE where difference in incidence between two arms $\geq 5\%$	59
Table 30 Laboratory tests	60
Table 31 Broad SMQ for Hematopoietic thrombocytopenia	63
Table 32 SMQ analysis for GI adverse events.....	63
Table 33 Preferred Terms in SMQ	63
Table 34 SMQ analysis	65
Table 35 Preferred terms in SMQ.....	65
Table 36 TEAE in Nervous System Disorders with a difference in incidence of $\geq 2\%$	65
Table 37 SMQ analysis for peripheral neuropathy	66
Table 38 TEAE included in Peripheral Neuropathy SMQ.....	66

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

Table 39 Broad SMQs cardiac related.....	66
Table 40 Broad SMQ for pulmonary toxicity	68
Table 41 TEAE for SMQ analysis of pulmonary hypertension	68
Table 42 TEAE in the system organ class of eye disorders	69
Table 43 Hypotension	69
Table 44 SMQ evaluation for Hepatic disorders.....	70
Table 45 Broad SMQ analysis for malignancy and premalignant disorders.....	71
Table 46 TEAE based on prior lines of therapy	72
Table 47 TEAE in N. America vs ROW	72
Table 48 TEAE Based on creatinine clearance	73
Table 49 TEAE with > 20% incidence of the Intergraded Safety Population (N=990)	74

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

Table of Figures

Figure 1 Kaplan-Meier Plot of PFS based on IRC assessment of ITT population	42
Figure 2 Kaplan Meier Plot of Overall Survival of ITT population.....	44
Figure 3 Average platelet count per visit.....	61
Figure 4 Average platelet count on the first day of each cycle	61

Glossary

ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BPI-SF	Brief Pain Inventory –Short Form
CI	Confidence Interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
Dex	dexamethasone
DSUR	Development Safety Update Report
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMWG	International Myeloma Working Group
IRC	independent review committee
LDH	lactate dehydrogenase
Len	lenalidomide
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NDA	new drug application
ORR	overall response rate
OS	overall survival
PFS	progression free survival
PK	pharmacokinetics
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
PRES	Posterior reversible encephalopathy syndrome
REMS	Risk Evaluation and Mitigation Strategy
SAE	serious adverse event
SMQ	Standardized MedDRA Query
TEAE	treatment emergent adverse events
VGPR	very good partial response

1 Executive Summary

1.1. Product Introduction

Ixazomib, proprietary name Ninlaro, is an oral proteasome inhibitor which reversibly binds and inhibits the 20S proteasome. The proposed starting dose is 4 mg taken orally on days 1, 8 and 15 of a 28 day cycle in combination with lenalidomide and dexamethasone. The indication to be approved is, “Ninlaro is a proteasome inhibitor indicated for the treatment of patients with multiple myeloma in combination with lenalidomide and dexamethasone who have received at least one prior therapy”. Ixazomib is a new molecular entity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness based on an improvement in progression free survival (PFS). This was demonstrated in a single, randomized, double-blind, clinical trial of 722 patients comparing the combination of ixazomib lenalidomide and dexamethasone to the combination of placebo, lenalidomide and dexamethasone. Results show an improvement in median PFS in the range of 4.1 months based on updated results, to 5.9 months based on the primary analysis.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Ixazomib is an oral proteasome inhibitor that reversibly binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome and induces apoptosis in the cell. The indication is, for the treatment of patients with multiple myeloma in combination with lenalidomide and dexamethasone who have received at least one prior therapy. Multiple myeloma is a plasma cell neoplasm in which, malignant plasma cells increase and produce a monoclonal immunoglobulin. The clinical features of multiple myeloma include depressed immunity and end-organ damage particularly in the kidneys, bone and hematopoietic system. Ixazomib is a new molecular entity that provides a new route of administration, oral, compared to currently approved proteasome inhibitors. The benefit risk assessment supports traditional approval for the indication.

Multiple myeloma is not a curable disease, with an average survival of approximately 6 years[1]. Treatment of multiple myeloma is multifaceted comprising of chemotherapeutic agents such as immunomodulating agents, proteasome inhibitors and alkylating agents, stem cell transplantation, and supportive measures such as bisphosphonates to prevent complications of the disease. A typical patient, progresses through several lines of therapy and, over the course of the disease, the periods of inactivity shorten. The patient may become non responsive to treatment and have morbidity and mortality associated with the disease, or the treatment itself. While the median survival of multiple myeloma has been improving, there still remains an unmet medical need and patients need new treatment options.

The benefit of ixazomib was demonstrated in a randomized, double-blind placebo controlled trial in patients with relapsed multiple myeloma who received 1 to 3 prior lines of therapy. A total of 722 patients were randomized to receive the combination of ixazomib, lenalidomide and dexamethasone or the combination of placebo, lenalidomide and dexamethasone. Progression free survival was 14.7 months (95% CI 12.9, 17.6) in the placebo arm to 20.6 months (95% CI; 17.0, NE) in the ixazomib arm. The stratified hazard ratio was 0.74 (95% CI 0.59, 0.94) with statistically significant p value of 0.013. The improvement in progressive free survival is abated somewhat with a subsequent non-inferential evaluation, however, there remains a clinically meaningful benefit. Another benefit of ixazomib, compared to currently approved proteasome inhibitors for multiple myeloma, is ixazomib is an oral medication. This may be more convenient for some patients.

The safety of ixazomib was evaluated in the trial mentioned above. The median number of cycles for both arms was 12 (range 1-26). The ixazomib combination arm was not associated with an increase in the rate of deaths within 30 days of the last dose of study drug compared to the placebo combination arm, 3.3% vs 4.7% respectively. A total of 144 patients (40.0%) on the ixazomib combination arm had at least one serious adverse event compared to 161 patients (44.8%) on the placebo combination arm. The serious adverse events that occurred in more

than 2% of patients overall are pneumonia (6.5% of all patients) and pyrexia (3.3% of all patients). The treatment emergent adverse events more common on the ixazomib arm, with a greater than 5% difference in incidence between the two arms, were vomiting, thrombocytopenia, constipation, peripheral edema, diarrhea and maculo-papular rash. It is necessary to acknowledge other adverse events increased on the ixazomib combination including peripheral neuropathy (38.9% vs 31.1% SMQ analysis), eye disorders (26.4% vs 15.8% for eye disorder system organ class), and hepatotoxicity (2.2% vs 0% SMQ analysis for drug related severe events only).

The primary efficacy benefit demonstrated was an improvement in progressive free survival on average of 4 to 6 months when ixazomib is added to lenalidomide and dexamethasone. This establishes substantial evidence of efficacy of ixazomib in multiple myeloma when used in combination with lenalidomide and dexamethasone. The risks demonstrated, mainly gastrointestinal disorders, rash, thrombocytopenia and cutaneous reactions are acceptable and do not outweigh the benefit. Ixazomib adds an additional treatment option with a different safety profile to the current armamentarium for the treatment of relapsed multiple myeloma. The recommendation is traditional approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Multiple myeloma is not a curable disease and is associated with morbidity and mortality. The typical course of multiple myeloma, as a patient progresses through treatment, is shortened periods of disease inactivity with the disease becoming unresponsive to treatment 	Relapsed multiple myeloma is a progressive and fatal disease.
Current Treatment Options	<ul style="list-style-type: none"> Current treatment options are not curative. Current treatments have toxicities that may limit use in certain patients. 	Effective therapy for multiple myeloma, with different safety profiles, are necessary to provide options to patients.
Benefit	<ul style="list-style-type: none"> In a double-blind, randomized, placebo controlled trial, ixazomib demonstrated an improvement in progression free survival of 4.1 to 5.9 months when added to lenalidomide and dexamethasone. No improvement in overall survival has been demonstrated. 	The addition of ixazomib to lenalidomide and dexamethasone improved progression free survival.
Risk	<ul style="list-style-type: none"> Treatment emergent adverse events increased with the addition of ixazomib were vomiting, thrombocytopenia, constipation, peripheral edema, diarrhea, maculo-papular rash and nausea. 	The overall safety profile is acceptable to the patient population.
Risk Management	<ul style="list-style-type: none"> Serious toxicities are manageable with dose reductions, dose delays and clinical and laboratory monitoring. 	The prescribing information will inform providers on adverse reactions and safe administration of ixazomib.

2 Therapeutic Context

2.1. Analysis of Condition

Multiple myeloma is characterized by the proliferation of immunoglobulin producing neoplastic plasma cells. Patients with multiple myeloma are characterized by production of a monoclonal antibody, depressed immunity, and end organ damage. The diagnosis of multiple myeloma involves end organ damage. This includes skeletal destruction with osteolytic lesions, osteopenia, and pathologic fractures, hypercalcemia, anemia, infections, and renal disease. Multiple myeloma is not considered a curable disease, although median survival has been improving [2]. The course of multiple myeloma for a typical patient involves periods of symptomatic disease requiring treatment followed by periods of remission. As patient progresses through different treatment regimens, periods of disease inactivity usually shorten and the disease ultimately becomes nonresponse to therapy which eventually leads to death.

2.2. Analysis of Current Treatment Options

Treatment of multiple myeloma is multifaceted. Chemotherapeutic agents target the neoplastic plasma cell, however, the management of multiple myeloma also includes preventing complications that are associated with morbidity and mortality. FDA approved therapy for multiple myeloma is displayed in Table 1. Management of multiple myeloma also involves adjunctive treatment such as bisphosphonates and in some cases, radiation.

Table 1 Approved therapy for multiple myeloma

Class	Drug	Year approved
Alkylating agents	melphalan	1964
	cyclophosphamide	1959
	carmustine	1977
Proteasome inhibitors	bortezomib	2003
	carfilzomib	2012
Immunomodulatory agents	lenalidomide	2006
	thalidomide	2006
	pomalidomide	2013
Anthracyclines	doxorubicin hydrochloride	2007
	liposome	
Histone deacetylase inhibitor	panobinostat	2015

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

Initial treatment of multiple myeloma normally involves the combination therapy of two to three chemotherapeutic agents. The choice of initial chemotherapy is dependent on factors, such as, risk stratification of the patient's disease, and if the patient is a candidate for hematopoietic stem cell transplantation. High dose chemotherapy followed by autologous stem cell transplantation is a standard of care for eligible patients.

Treatment of relapsed disease depends on multiple factors as well. Options for relapsed or refractory disease include hematopoietic stem cell transplantation, rechallenging the patient with previously used agents, new chemotherapeutic options, or some combination of previously used and new agents. As mentioned in section 2.1, the patient may progress through several lines of therapy and the disease becomes nonresponsive to treatment.

Ixazomib is an oral proteasome inhibitor. As displayed in Table 1, there are two proteasome inhibitors currently approved. Bortezomib, received accelerated approval in 2003 for multiple myeloma patients who have received at least two prior therapies based on a single arm trial which demonstrated an ORR (overall response rate) of 28%. In 2005, bortezomib was approved for the treatment of multiple myeloma patients who received at least one prior therapy. This was based on a randomized controlled trial of bortezomib compared to high dose dexamethasone in patients with progressive multiple myeloma following 1 to 3 prior therapies. The time to progression was 6.2 months in the bortezomib arm compared to 3.5 months in the dexamethasone arm with a hazard ratio of 0.55 (95% CI 0.44, 0.69; p value <0.0001). An OS (overall survival) benefit was demonstrated as well. In 2008, the indication was changed to the treatment of patients with multiple myeloma, the requirement of prior therapies was removed. This was based on a randomized controlled trial of bortezomib + melphalan + prednisone compared to melphalan + prednisone. The bortezomib arm demonstrated improvement in progression free survival of 18.3 months compared to 14.0 months, with a hazard ratio of 0.61 (95% CI 0.49, 0.76; p value =0.00001). An OS benefit was demonstrated as well.

Carfilzomib, the other proteasome inhibitor currently approved, initially received accelerated approval in 2012 for the treatment of patients who received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. This approval was based on an ORR of 22.9% (95% CI: 18.0, 28.5) in a single-arm trial. The median duration of response was 7.8 months (95% CI: 5.6, 9.2). Carfilzomib received traditional approval in 2015 in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who received one to three prior lines of therapy. This approval was based on a randomized, open-label, multicenter trial evaluating carfilzomib + lenalidomide + low-dose dexamethasone compared to lenalidomide + low-dose dexamethasone in patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy. The median PFS in the carfilzomib arm was 26.3 months (95% CI 23.3 to 30.5 months) compared to 17.6 months

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

(95% CI: 15.0 to 20.6 months) in the lenalidomide and low-dose dexamethasone arm (HR = 0.69, with a 2 sided p-value =0.0001).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Ixazomib is a new molecular entity and not currently marketed in the U.S.

3.2. Summary of Pre-submission/Submission Regulatory Activity

Table 2 Interactions with FDA

Interaction	Date	Details
Submitted IND	April 2009	
End of phase 2 meeting	November 2011	
Advice request	February 2012	Applicant requested additional advice on PRO and Quality of Life Assessments
Type C meeting	April 2014 May 2014	Topics include NDA format and content. Sponsor response
IRT advice	August 2014	
Type C meeting	November 2014 January 2015	Topics related to NDA format and content Sponsor response
Proprietary name	December 2014	Conditional proprietary name approval for Ninlaro
Type B meeting pre NDA	April 2015	Discussion of regulatory, clinical and pharmacovigilance aspects of NDA

End of phase 2 meeting November 14, 2011

The purpose of this meeting was to seek advice on the design of the phase 3 randomized trial comparing lenalidomide and dexamethasone with and without ixazomib. The concerns regarding the endpoint of PFS, including imbalance in assessment dates, missing data and unblinding due to toxicities was discussed. It was also discussed that the magnitude of PFS improvement will remain a review issue. The design of the trial including one PFS analysis at the first interim analysis was discussed. The Agency recommended conducting a non-inferential post-final analysis on PFS at the time of second interim OS analysis. The Agency agreed that ORR, OS, and OS in high risk patients positive for the del(17) biomarker are appropriate key secondary endpoints. The Agency agreed with the choice of comparator. The Agency expressed concern regarding the dose selected as only 3 patients had been treated at the proposed dose. The applicant responded to this concern that the phase 2 cohort of trial

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

C16005 will be fully enrolled prior to the initiation of the C16010 trial. It was discussed that this data should be submitted prior to the start of the phase 3 trial.

The instruments of Brief Pain Inventory – Short Form and analgesic use, the quality of life measured by patient-reported outcome questionnaires including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the multiple myeloma specific module (QLQ-MY-20) were discussed. Several concerns were discussed and the applicant expressed an interest to further discuss in a subsequent meeting.

Type C Written Responses February 13, 2014

The purpose of the meeting was to provide feedback regarding the NDA submission. The topics for this interaction included the Integrated Summary of Efficacy, Integrated Summary of Safety, submission of the data for the renal and hepatic impairment studies, individual patient narratives, and format of clinical and non-clinical data sets.

During this meeting it was agreed that the Integrated Summary of Efficacy will not be included. It was recommended the sponsor include patients who received IV ixazomib as a separate cohort. It was also mentioned that interim study results should be included in the NDA submission or during the review cycle only if there is a serious safety signal that needs to be addressed in labeling. Narratives for all adverse events of death, SAEs (serious adverse event), discontinuations due to TEAEs and other significant AEs of interest were to be included.

Type C Written Responses October 16, 2014

This was the second Type C Written Response related to NDA content and format. Topics addressed in this interaction include patient narratives and case report forms, adverse events of clinical importance for patient narratives, Summary of Clinical Efficacy, marginal structural models for the primary analysis of overall survival, content and format of site-level clinical data, financial disclosure information, and Question-Based Review Clinical Pharmacology Summary.

The applicant was informed to submit narratives of patients with event of special interest including peripheral neuropathy, encephalopathy, hypotension and cardiac toxicity. For rash and hepatic toxicity, narratives for grade 2 or higher events were to be submitted. The strategy of the summary of clinical efficacy was addressed.

Type B Meeting pre NDA April 1, 2015

Topics discussed include the general submission plan for the clinical efficacy and safety sections of the NDA, the 120 day safety update, the submission plan of C16009 (drug-drug interaction, food effect, relative bioavailability) study data, possible REMS approach, data from the second interim analysis for the pivotal Study C16010, the Applicant Orientation Meeting and the timing of submission of the structured product labeling.

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

3.3. **Foreign Regulatory Actions and Marketing History**

From the DSUR covering March 29, 2014 to March 27, 2015, ixazomib does not currently have marketing authorization in any country. The design of the pivotal study C16010, per applicant, was discussed with the European Medicines Agency as well. In Europe, orphan designation for the treatment of MM was granted by the European Commission.

4 **Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

4.1. **Office of Scientific Investigations (OSI)**

The Office of Scientific Investigations conducted inspections for protocol C16010 at clinical sites in Hackensack, New Jersey (Site #58011), and in Budapest, Hungary (Site #22003). These sites were chosen based on high accrual or concern for financial conflict. The preliminary results of the inspections were voluntary action indicated, meaning there were deviations from regulations however, the data was acceptable. The applicant was inspected and no deviation from regulation was found and data was determined to be acceptable.

4.2. **Product Quality**

The recommendation, from a product quality perspective, is approval pending an approval facility recommendation. The statement "A 36 month shelf life is granted for Ixazomib capsules stored at room temperature not to exceed 30°C (86°F)." is to be included in the action letter. There are no product quality post marketing commitments or agreements.

4.3. **Clinical Microbiology**

Clinical microbiology is not relevant to this application.

4.4. **Nonclinical Pharmacology/Toxicology**

Ixazomib is a proteasome inhibitor. Ixazomib reversibly binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome and induces caspase mediated apoptosis in multiple myeloma cells. Nonclinical findings demonstrate that ixazomib specifically targets the gastrointestinal and lymphoid systems. Dose limiting toxicities in the rats and dogs were primarily a result of effects in the gastrointestinal and lymphoid systems. Neuronal degeneration of the sympathetic dorsal root and end organ ganglia were seen in dogs.

Ixazomib was determined to be teratogenic and embryo-lethal as well as genotoxic. Ixazomib is not mutagenic. An in vitro chromosomal aberration assay in human peripheral blood

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

lymphocytes, ixazomib tested positive for inducing structural chromosome aberrations. Carcinogenicity studies were not conducted.

4.5. **Clinical Pharmacology**

The submitted NDA data support approval of ixazomib for the proposed patient population from a clinical pharmacology perspective at the proposed dosing regimen, provided an agreement is reached for labeling language.

4.5.1. **Mechanism of Action**

Ixazomib is a selective and reversible proteasome inhibitor. It binds and inhibits the chymotrypsin-like activity of the $\beta 5$ site ($IC_{50}=3.4$ nM), and to a lesser extent $\beta 1$ ($IC_{50}=31$ nM), and $\beta 2$ site ($IC_{50}=3500$ nM), of the 20S proteasome. This leads to disruption of cellular regulatory mechanisms and death of the cell.

4.5.2. **Pharmacodynamics**

There were no significant exposure-response relationships for efficacy including the primary endpoint of PFS. Significant exposure-response relationships for safety were observed for major adverse events including grade 3+ thrombocytopenia, grade 2+ rash and grade 2+ gastrointestinal toxicities.

4.5.3. **Pharmacokinetics**

Following oral administration, ixazomib is rapidly absorbed with a median T_{MAX} of 1 hour. Following multiple-dose administration, plasma exposure generally increased over a dose range of 0.48 to 3.95 mg/m². 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. Hepatic and renal impairment studies showed that ixazomib systemic exposure was increased by 13-42% in patients with moderate to severe hepatic impairment and in patients with severe renal impairment to end stage renal disease requiring dialysis compared to patients with normal hepatic and renal function.

4.6. **Devices and Companion Diagnostic Issues**

Devices and companion diagnostic issues are not relevant to this application.

4.7. **Consumer Study Reviews**

The Division of Medication Error Prevention and Analysis reviewed the proposed Prescribing Information and proposed carton labels. Based on recommendations, changes were made to foster safe use and decrease medication errors.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 is a list of some of the clinical trials submitted with the application. Not included are phase 1 studies to characterize the PK and PD, drug drug interaction studies, trials done in specific populations including renal and hepatic impairment patients, and trials done to characterize the PK in Asian and Japanese patients. Study C16010CCS, a China continuation study, which is currently ongoing and similar design to study C16010, is not included in Table 3. The applicant also has ongoing studies in other diseases, including amyloidosis and relapsed or refractory lymphoma and ongoing studies in newly diagnosed multiple myeloma, which are not listed.

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

Table 3 List of Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
C16010	Phase 3, randomized, double blind, placebo controlled	Ixazomib 4 mg or placebo QW for 3 weeks (days 1, 8, 15) + Len 25 mg (Days 1-21) and dex 40 mg (days 1, 8, 15, 21) in 28 day cycle Len start dose 10 mg if CrCl is \leq 60mL/min (or 50mL/min according to local practice); escalation to 15 mg if tolerated	PFS, safety of ixazomib + LenDex vs placebo + LenDex	Treatment until PD or unacceptable toxicity	722	Adult patients with RRMM after 1-3 prior lines of therapy	147 Global
<i>Clinical Studies Contributing to Dose Selection</i>							
C16001	Phase 1, open label, dose escalation, first-in-human, with MTD disease expansion & tumor PD expansion	Ixazomib: IV injection, twice weekly for 2 wk (Days 1, 4, 8, 11) in 21 day Escalation start dose=0.125 mg/m ² IV. MTD/PD expansion dose=1.76 mg/m ² IV	Safety, MTD, RP2D of ixazomib (IV injection)		116	Adult patients with nonhematologic malignancies for which no effective standard treatment was available or did not offer curative or life-prolonging potential	7 U.S., Canada
C16002	Phase 1, open label, dose escalation	Ixazomib IV QW for 3 wk (days 1, 8, 15) in 28 day cycles. Escalation start dose=0.125 mg/m ² IV. MTD/expansion	Safety, MTD, RP2D of ixazomib (IV injection)		30	Adult patients with lymphoma, \geq 2 lines prior therapy, and for which no curative therapy exist.	7 U.S., Canada

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

		dose=2.34 mg/m ² IV					
C16003	Phase 1, open label, dose escalation, MTD expansion	Ixazomib twice weekly for 2 wk (days 1, 4, 8, 11) in 21 day cycles Escalation start dose=0.24 mg/m ² MTD/expansion dose=2.0 mg/m ²	Safety, tolerability, MTD, RP2D of oral ixazomib (twice weekly)	Up to 12 cycles, beyond 12 cycles allowed if clinical benefit	60	Dose escalation: Adult patients with relapsed refractory MM, ≥2 lines prior therapy including bort, thal or len, and corticosteroids MTD expansion: Adult with relapsed refractory MM ≥1 line prior therapy; refractory to last line; prior carfilzomib; PI-naïve or relapsed after bort treatment.	5-US
C16004	Phase 1, open label, dose escalation, MTD expansion	Ixazomib QW for 3 wk (days 1, 8, 15) in 28-day cycles for up to 12 cycles. Escalation start dose=0.24 mg/m ² MTD/expansion=2.97 mg/m ²	Safety, tolerability, MTD of oral ixazomib (QW dosing)	Treatment beyond 12 cycles allowed if patient deriving benefit and would continue until PD or unacceptable toxicity	60	Dose escalation: Adult with relapsed refractory MM; ≥2 lines prior therapy that included bort, thal or len, and corticosteroids MTD expansion: Adult with relapsed refractory MM ≥1 line prior therapy; refractory to last line; prior calfilzomib; PI-naïve or relapsed after bort	6-US
C16005	Phase 1/2, open label, induction &	Induction (12 cycles): Ixazomib QW (days 1, 8,	Phase 1: safety,		65	Adult patients with newly diagnosed	10-US

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

	maintenance, dose escalation and treatment at RP2D.	15) + dex 40 mg (days 1, 8, 15, 22) + len 25 mg (days 1-21) 28 day cycle Ph 1: escalation start dose=1.68 mg/m ² . MTD=2.97 mg/m ² Ph 2: 4.0 mg fixed dose Maintenance (cycles ≥13): Patients with ≥SD may continue on single-agent ixazomib once weekly for 3 wk (days 1, 8, 15) in 28 day cycles at dose tolerated at end of induction until PD or unacceptable toxicity	tolerability, MTD, RP2D of ixazomib QW + LenDex Phase 2: Efficacy (CR + VGPR), safety, tolerability of ixazomib QW + LenDex			requiring systemic treatment (ASCT eligible or ineligible)	
--	---	---	--	--	--	--	--

Abbreviations: ASCT=autologous stem cell transplantation; bort=bortezomib; CR=complete response; CrCl=creatinine clearance; Dex=dexamethasone; Len=lenalidomide; IV=intravenously; MM=multiple myeloma; MTD= maximum tolerated dose; PD=progressive disease; PFS=progression free survival; PI=proteasome inhibitor; QW=once weekly; RP2D=recommended phase 2 dose; RRMM=relapsed refractory multiple myeloma; thal=thalidomide; VGPR=very good partial response; wk=weeks

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

5.2. Review Strategy

The clinical review was conducted by a single reviewer. Trial C16010 served as the primary basis for the review. Safety and efficacy data, including data tabulation and data analysis datasets, and the clinical study report was reviewed. In order to reproduce key efficacy and safety analyses and for additional exploratory analysis JMP, JReview and MAED were used.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. 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

6.1.1. Study Design

The primary objective was to determine whether the addition of ixazomib to the background of lenalidomide and dexamethasone improves PFS in patients with relapsed and/or refractory multiple myeloma.

Key secondary objectives include determining if the addition of ixazomib improves OS and OS in high-risk patients with del(17).

Other objectives include

- To determine ORR, including PR (partial response), VGPR (very good partial response) and CR (complete response)
- To determine CR + VGPR
- To determine duration of response
- To determine time to progression
- To determine the safety of the addition of ixazomib to lenalidomide and dexamethasone
- To determine pain response rate, assessed by BFI-SF and analgesic use
- To assess change in global health status, functioning, and symptoms as measured by the patient-reported outcome instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and MY-20 module
- To determine the PFS and OS in high risk cytogenetic patient groups such as translocations t(4;14), t(14;16), +1q, del(13), or del(17)
- To evaluate the potential relationship between response or resistance to ixazomib treatment and (b) (4) in proteasome and nuclear factor- κ B related genes, such

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

as proteasome subunit beta type-1 and tumor necrosis factor receptor-associated factor-3, or proteasome levels in plasma

- To evaluate the potential relationship between response or resistance to ixazomib treatment and mutations in key signaling pathways
- To collect PK data to contribute to population PK analyses

Trial Design

This is a phase 3, randomized, double-blind multicenter study to evaluate safety and efficacy of ixazomib versus placebo in patients with relapsed and/or refractory multiple myeloma who were treated with lenalidomide and dexamethasone as their standard therapy. Patients treated with lenalidomide plus dexamethasone were randomized 1:1 to receive ixazomib or placebo in a double-blind fashion. Patients were stratified by 1 versus 2 or 3 prior lines of therapy, proteasome-inhibitor exposed versus naïve, and International Staging System stage at screening of 1 or 2 versus 3.

Patients received ixazomib 4 mg or placebo on days 1, 8 and 15, lenalidomide 25 mg on days 1 through 21, and dexamethasone 40 mg on days 1, 8 and 15 and 22 of a 28 day cycle. Patients continued treatment until progression disease or unacceptable toxicity. Dose modifications were allowed based on toxicities. Patients with creatinine clearance of 30 to 50 mL/min received lenalidomide 15 mg once daily, and after 2 cycles, if the patient was not responding, may have been escalated to 15 mg. Patients were seen twice a treatment cycle, defined as 28 days, for the first 3 cycles, then once a treatment cycle while receiving active treatment.

Patients were assessed for disease response and progression by an independent review committee. Response was evaluated according to the IMWG (International Myeloma Working Group) criteria every 4 weeks until disease progression. All patients, after progression, were to be followed for survival. Patients were to be contacted every 12 weeks until death or termination of the study.

Toxicities were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Each adverse event should have been attributed to a specific drug, so dose modifications can be made. Reduction of one agent was appropriate; however, reduction of multiple agents was permitted for overlapping toxicities.

Dose adjustments were allowed for ixazomib based on clinical and laboratory evaluation. The starting dose was 4.0 mg, the first reduction 3.0 mg and second reduction 2.3 mg and the third reduction was discontinuation of the study drug.

As specified in the protocol, for the overlapping toxicities of thrombocytopenia, neutropenia and rash, an alternating reduction schedule was used for ixazomib and lenalidomide. The dose

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

adjustment schedule used for thrombocytopenia, neutropenia and rash is discussed in section 8.4.3.

Dose Adjustments for Ixazomib

Dose modification of ixazomib was recommended for peripheral neuropathy. For grade 1 peripheral neuropathy, no action was to be done. For grade 1 peripheral neuropathy with pain or grade 2, ixazomib was to be held until resolution to \leq Grade 1 or baseline. For grade 2 peripheral neuropathy with pain or grade 3 peripheral neuropathy, ixazomib was to be held until resolution to \leq grade 1 or baseline and ixazomib was to be reduced to the next lower dose. For grade 4 peripheral neuropathy, ixazomib was to be discontinued.

For non-hematologic toxicities, judged to be related to ixazomib, dose adjustment guidelines were specified in the protocol. For grade 3 ixazomib was to be held until resolution to grade < 1 or baseline. If the toxicity did not recover to $< \text{grade } 1$ or baseline within 4 weeks, lenalidomide was to be held until resolution to grade < 1 or baseline and the ixazomib was to be reduced to next lower dose upon return to $< \text{grade } 1$ or baseline. For subsequent recurrence grade 3 that does not recover to $< \text{grade } 1$ or baseline within 4 weeks, ixazomib and lenalidomide was to be held until resolution to grade < 1 or baseline and ixazomib as well as lenalidomide was to be reduced one dose level. For grade 4 nonhematologic toxicities judged to be related to study drug the recommendation was to permanently discontinue ixazomib, except in a case where the investigator determines the patient is obtaining a clinical benefit.

Before beginning the next cycle of treatment, the patient was to meet the criteria of absolute neutrophil count $\geq 1,000/\text{mm}^3$, platelet count $\geq 75,000/\text{mm}^3$, or other non-hematologic toxicities \leq grade 1 or to the patient's baseline condition. For a delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery, absolute neutrophil count $< 1,000/\text{mm}^3$, platelet count $< 75,000/\text{mm}^3$, or other non-hematologic toxicities $> \text{grade } 1$ or not to the patient's baseline condition, ixazomib was to be held until resolution and reduced to the next lower dose level. The maximum delay before treatment should have been discontinued was to be 3 weeks, except in the case of investigator determined clinical benefit.

Dose Adjustment Guidelines for Lenalidomide

The starting dose of lenalidomide was 25 mg, the first dose reduction was 15 mg, the second dose reduction was 10 mg and the third dose reduction was 5 mg. For grade 3 and 4 toxicities judged to be related to lenalidomide, lenalidomide was to be held and restarted at the next lower dose level when toxicity had resolved to \leq grade 2. For renal dysfunction the dose reduction was to be done per lenalidomide package insert or SmPC (summary of product characteristics). For thrombosis/embolism \geq grade 2, lenalidomide was to be held, and anticoagulation therapy was to be started. Lenalidomide was to be restarted at investigator's discretion. For any grade angioedema, grade 4 exfoliative or bullous rash or if Stevens-Johnson Syndrome was suspected, lenalidomide was to be permanently discontinued. For grade 2 or 3

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

skin rash lenalidomide was to be held or discontinued per package insert or SmPC. For tumor lysis, the dose of lenalidomide was to be modified per lenalidomide package insert or SmPC.

Dose Adjustment Guidelines for Dexamethasone

The starting dose of dexamethasone was 40 mg, the first dose reduction was 20 mg, the second dose reduction was 8 mg and the third dose reduction was to discontinue dexamethasone. For grade 1 and 2 gastrointestinal symptoms, treatment was to be with symptomatic measures and if symptoms persist the dose of dexamethasone was to be decreased by 1 dose level. For grade greater than 3, requiring hospitalization or surgery, dexamethasone was to be held until symptoms were controlled and the dose was to be decreased by one dose level and treatment with histamine-2 blockers, sucralfate or omeprazole administered. If symptoms persisted, dexamethasone was to be discontinued and not restarted. For acute pancreatitis, dexamethasone was to be discontinued and not resumed.

For edema > grade 2, diuretics were to be used and dexamethasone was to be decreased by 1 dose level. If the edema persisted, another dose reduction of dexamethasone was to be done. If the symptoms persisted despite the second reduction, dexamethasone was to be discontinued.

For confusion or mood alteration > grade 2, dexamethasone was to be held until symptoms resolve and restarted with 1 dose level reduction. If symptoms persist despite this, dexamethasone was to be discontinued.

For muscle weakness > grade 2 dexamethasone was to be decreased by 1 dose level. If the weakness persisted, the dose was again to be decreased by 1 dose level. If symptoms persist, dexamethasone was to be discontinued.

For hyperglycemia > grade 3, treatment was to be initiated with insulin or hypoglycemic agents. If uncontrolled, the dose was to be decreased by 1 dose level until glucose levels were satisfactory.

Inclusion Criteria

- Man and woman \geq 18 years of age
- Multiple myeloma with symptomatic disease at initial diagnosis
- Measurable disease defined by at least one criteria
 - Serum M protein \geq 1 g/dL
 - Urine M-protein \geq 200 mg/24 hours
 - Serum free light chain assay: involved free light chain \geq 10 mg/dL, provided serum free light chain ratio is abnormal
- Patients with relapsed and/or refractory multiple myeloma who have received 1 to 3 prior therapies.

Clinical Review

Alexandria Schwarsin, MD

NDA 208462

Ninlaro (ixazomib)

- This includes patients who relapsed but were not refractory, patients who were refractory to all lines of previous treatment and patients who relapsed from 1 and were refractory to at least one previous treatment. Refractory disease is defined as disease progression within 60 days after the last dose of treatment.
- A line of therapy is defined as 1 or more cycles of a planned treatment program. This consists of 1 or more cycles of single-agent or combination, or sequence of treatments. A planned induction, transplant followed by maintenance is considered 1 line of therapy. Autologous and allogenic transplants are permitted.
- Patients must have met the following laboratory criteria:
 - $ANC \geq 1000/mm^3$ and platelet count $\geq 75,000/mm^3$. Platelet transfusions to help patients meet eligibility criteria were not allowed within 3 days prior to randomization.
 - Total bilirubin ≤ 1.5 x the upper limit of the normal range
 - Alanine aminotransferase and aspartate aminotransferase ≤ 3 x upper limit of the normal range
 - Calculated creatinine clearance ≥ 30 mL/min
- Additional criteria include ECOG (Eastern Cooperative Oncology Group) status of 0, 1, or 2, and for patients with prior allogenic transplant no active graft versus host disease.
- For female patients of childbearing potential must agree to practice 2 effective methods of contraception from 28 days prior to starting study drug through 30 days after the last dose of treatment or agree to abstain from heterosexual intercourse. Male patients, even if sterilized, must agree to abstain from heterosexual intercourse or practice an effective barrier contraception during treatment and through 4 months after the last dose. Patients must also adhere to the guidelines of the lenalidomide pregnancy prevention program.
- Patients must be able to take aspirin 325 mg daily or enoxaparin 40 mg SQ daily as prophylactic anticoagulation. For patients with a history of DVT (deep venous thrombosis), low molecular weight heparin is mandatory.
- Voluntary written informed consent.
- Patients must have been able to be compliant with the study schedule.

Pertinent exclusion criteria

- Patient's refractory to lenalidomide or proteasome inhibitor based therapy. Refractory is defined as disease progression within 60 days of last dose. Patients refractory to thalidomide were eligible.
- Failure to have recovered, < Grade 1 toxicity from prior therapy
- Major surgery, radiotherapy, infection requiring systemic antibiotic treatment, or other serious infection within 14 days prior to randomization.
- Central nervous system involvement
- Diagnosis of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy,

organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome or myeloproliferative syndrome.

- Uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina or myocardial infarction within 6 months.
- Ongoing or active systemic infection including active hepatitis B or C, or known HIV.
- Treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days.
- Systemic illness or concurrent disease which would have made the patient inappropriate for the trial.

Study Endpoints

The primary endpoint is PFS defined as the time from the date of randomization to the date of first documentation of disease progression based on central laboratory results and IMWG criteria evaluated by an independent review committee or death due to any cause, whichever is first. Progressive disease confirmation is required by 2 consecutive evaluations, at least 1 week apart, as per IMWG criteria.

The key secondary endpoints are:

- OS, measured from date of randomization to the date of death
- OS in high-risk patients carrying del(17)

Other secondary endpoints are:

- Overall response rate (CR + VGPR + PR)
- CR + VGPR rate
- Duration of response, measured as the time from the date of first documentation of response to the date of first documented progression
- Time to progression, measured as the time from randomization to the date of first documented progression
- ECOG performance scores, AEs, SAEs, and assessments of clinical laboratory values
- Pain response rate, measured by the proportion of pain responders, as determined by the BFI-SF and analgesic use
- Comparison of change in global health status between baseline and each post baseline assessment, as measured by the global health scale, functioning, and symptoms of the EORTC QLQ-C30 and MY-20
- OS and PFS in high-risk population carrying del(13), del(17), +1q21, t(4;14), or

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

t(14;16)

- Association between response or resistance to ixazomib treatment and (b) (4) in proteasome and nuclear factor- κ B related genes, such as proteasome subunit beta type-1 and tumor necrosis factor receptor associated factor-3, or circulating proteasome levels
- Association between response and resistance to ixazomib treatment or mutations in key pathways.
- Plasma concentration-time data to contribute to future population PK analysis

Statistical Analysis Plan (summary from Statistical Review and Evaluation by Yun Wang, PhD)

The Statistical Analysis Plan specifies this was a phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of ixazomib versus placebo in patients with relapsed or refractory multiple myeloma who were treated with lenalidomide and dexamethasone as standard therapy. The population was adults with multiple myeloma who received 1 to 3 prior lines of therapy. Patients were randomized in a 1:1 ratio to either ixazomib or placebo in a double-blind fashion. Patients were stratified by 1 versus 2 or 3 prior therapies, proteasome-inhibitor exposed versus naïve, and International Staging System stage at screening of 1 or 2 versus stage 3.

The intent to treat population, defined as all patients randomized analyzed according to the treatment the patient was randomized to, were to be used for the primary and secondary efficacy analyses. The safety population was defined as all patients who received at least one dose of study drug, analyzed according to the treatment received. The safety population was to be used for all safety related analyses.

There is one primary endpoint, PFS and 2 key secondary efficacy endpoints, OS and OS in high risk patients carrying deletion 17.

In the original protocol, there was one and only analysis for PFS, which was planned at 234 PFS events. With amendment 3 dated 08 July 2014, timing for PFS analysis was revised, one interim efficacy analysis of PFS was added at ~ 262 PFS events, and the final PFS analysis was changed to when ~365 PFS events occur. Lan-DeMets spending function with O'Brien Fleming boundary was used to determine superiority boundaries for both interim and final PFS analyses.

In the original protocol, the sample size was calculated based on maintaining 80% power to test the first key secondary endpoint OS. There were two interim and one final analyses planned for OS at ~118, ~322, and ~482 deaths respectively. Assuming a hazard ratio of 0.77 (median survival of 30 months in placebo arm versus 39 months in Ixazomib arm), a total of approximately 703 patients would be needed to test OS with 80% power and 2-sided type I error rate of 5%, assuming an average enrollment rate of approximately 13 patients/month for

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

the first 6 months, 30 patients/month thereafter, and approximately 10% dropout rate. With 234 PFS events, it will have 90% power to detect a hazard ratio of 0.66 (median PFS of 11 months for placebo versus 16.8 months for ixazomib) with a 2-sided alpha level of 0.05.

In protocol amendment 3, the sample size was the same but the assumption for sample size justification was revised according to the latest research findings. The assumed median PFS was revised to 15 months for the placebo arm and 20.6 months for the ixazomib arm, the assumed HR was revised to 0.728, and the power for PFS analysis was reduced to 85%. The power analysis for OS in amendment 3 was similar to that in original protocol, except that there would be 3 interim and 1 final analyses of OS at ~154, ~222, ~322, and ~486 deaths respectively.

Protocol Amendments

The original protocol was finalized on February 21, 2012. The protocol was amended 4 times. Amendment 2 and 4 were continuation amendments for China only and are not discussed. A total of 138 patients were enrolled under the original protocol. Amendment 1 was dated September 14, 2012 and was to address regulatory feedback and clarify inconsistencies in the protocol. The pertinent changes are summarized below. Following Amendment 1 the remaining 584 patients were enrolled. Amendment 3 was dated July 8, 2014. The primary purpose of Amendment 3 was to change to the planned primary statistical and quantitative analyses, to add an additional PFS analysis, which was to be considered the final analysis. The original planned first interim analysis was to be conducted at a later date when approximately 262 PFS events had occurred. The added PFS analysis, the new final analysis, was to be conducted when approximately 365 PFS events had occurred. If the PFS at the first interim analysis was statistically significant, the PFS at the final analysis was a non-inferential test only. The 2 PFS analyses also served as the first interim analysis and second interim analysis for overall survival. Also in amendment 3, the assumption on median PFS for both arms was updated for the sample size calculation.

Amendment 1

- Volume of water taken with study drug was increased from 150 mL to 240 mL
- Palliative radiotherapy for pain control in a preexisting lesion may be considered
- Updated management of erythematous rash to include Stevens-Johnson syndrome
- Updated management of thrombocytopenia to include Thrombotic Thrombocytopenic Purpura
- Clarify management of fluid deficit, and that nonsteroidal anti-inflammatory drug intake before ixazomib should be discouraged
- Added the clinical management of hypotension and PRES (posterior reversible encephalopathy syndrome)
- Added thyroid testing and additional hematology testing to align with lenalidomide SmPC

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

- Clarify pain assessments and change skeletal survey frequency
- Clarify assessments for patients with extramedullary disease
- The cost assessment section was removed
- Clarify bone marrow aspirate is used to confirm CR or PD
- Removed requirement for bone marrow biopsy
- Clarify radiographic disease assessments were to be every 8 weeks during the follow-up period
- Correct the role of the IDMC (Independent Data Monitoring Committee)
- Update the version of IMWG uniform response criteria from 2006 to the 2011 version

Amendment 3

- The statistical and quantitative analysis sections were updated to include assumptions on PFS for sample size calculation and additional interim analysis.
- Two biomarker objectives were moved to exploratory objectives
- The timing of the EuroQol 5-Dimensional Health Questionnaire and skeletal survey were clarified.
- Clarified that during the PFS follow-up, patients were to be seen every 4 weeks and every 12 weeks during the OS follow-up phases
- Added that alternative dose modifications must be approved by the applicant
- Information regarding rash was added, the type of rash seen and management. Biopsy of grade 3 or higher rash or any SAE involving rash was recommended.
- It was added that growth factor support may be considered for neutropenia.
- It was clarified that fluid deficit should be corrected before initiation of study drug to avoid dehydration.
- It was added that one case of transverse myelitis was reported.
- The role of central and local laboratories was clarified.
- It was updated that an applicant clinician will review source data documenting disease progression prior to the investigator stopping disease assessments for progressive disease or taking the patient off treatment.
- Prior to the investigator taking the patient off treatment, the investigator is required to submit the rationale to the applicant clinician for review.
- Clarified that the ITT population will be used for patient-reported outcome assessments.
- Added that the independent data monitoring committee will receive reports of new primary malignancies during the study.
- Clarified the IMWG response criteria for VGPR in terms of plasmacytoma

Data Quality and Integrity: Applicant's Assurance

The applicant stated that quality-control checks are done on all clinical studies that the applicant sponsors. The clinical study report states that clinical investigator site audits were

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

performed during the study. During visits, information recorded on the eCRFs, was verified against source documents.

6.1.2. Study Results

Compliance with Good Clinical Practices

The clinical study report contains the following statement:

This study was performed in accordance with Good Clinical Practice, according to the ICH (International Conference on Harmonization) final guideline (01 May 1996) and including the archiving of essential documents. This report was prepared according to the ICH E3 clinical study report guidelines.

Financial Disclosure

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

The applicant submitted the financial disclosure and certifications for the trial. There were financial conflicts of interest reported from some investigators. The financial interests do not appear to affect the integrity of the application for several reasons. This includes, the trial was double-blind placebo controlled, an IRC reviewed results for efficacy, and there did not appear to be a correlation between the compensation received and the number of patients enrolled. See Appendix for Clinical Investigator Financial Disclosure Review.

Patient Disposition

A total of 722 patients were enrolled and randomized, 360 to the ixazomib arm and 362 to the placebo arm. Two patients randomized to the ixazomib arm never received any study drug, patient 18009-002 withdrew consent and patient 46004-001 had a serious pretreatment AE. As a result, these two patients in the ITT population were excluded from the safety analysis. Two patients initially randomized to the placebo arm were given ixazomib during treatment and thus, are included in the safety population for the ixazomib arm.

The disposition of the ITT population is displayed in Table 4. More patients on the placebo arm discontinued treatment, 48.3% on the placebo arm compared to 44.7% on the ixazomib arm. The percentage of patients discontinuing study treatment secondary to an adverse event was similar in the two arms, 12.8% in the ixazomib arm compared to 11.0% in the placebo arm. The percentage of patients discontinuing secondary to progressive disease was only slightly higher on the placebo arm, 29.3% compared to 23.3% on the ixazomib arm.

Regarding the other category in Table 4, 13 patients on the ixazomib arm discontinued as a result of patient decision, but agreed to follow up in PFS or OS, 4 patients were planning on proceeding to stem cell transplantation and 1 patient was listed as physician and patient decision. Regarding the remaining two patients in the other category for the ixazomib arm, one never received drug secondary to serious pretreatment adverse event and another had progressive disease by local standards. The reasons for discontinuation in the other category in Table 4 on the placebo arm are, 1 patient started another regimen, 1 patient decided to discontinue secondary to declining health status, 1 was planning for a stem cell transplant, 10 patients decided to discontinue but were willing to continue with either PFS or OS follow up, 1 was determined to have progressive disease by the investigator but not confirmed by IMWG criteria, 1 patient withdrew consent and another refused to continue.

Table 4 Patient Disposition

	Ixazomib + LenDex N(%)	Placebo + Len Dex N(%)
ITT population	360	362
Safety population	360	360
Continuing on treatment	199 (55.3)	187 (51.7)

	Ixazomib + LenDex N(%)	Placebo + Len Dex N(%)
Discontinued Study treatment	161 (44.7)	175 (48.3)
Reason off Study		
Adverse event	46 (12.8)	40 (11.0)
Progressive Disease	84 (23.3)	106 (29.3)
Patient withdrew	9 (2.5)	11 (3.0)
Protocol Violation	0 (0)	1 (0.3)
Lost to follow up	2 (0.6)	0 (0)
Other	20 (5.6)	16 (4.4)

Protocol Violations/Deviations

Based on the safety population, a total of 18 patients (5%) on the ixazomib + LenDex arm had at least one major protocol violation compared to 14 patients (3.9%) on the placebo + LenDex arm. The types of protocol deviations are listed in Table 5. For inclusion and exclusion protocol deviations, as the deviation was determined after the patient started treatment, the patients remained on protocol. In the ixazomib arm, inclusion and exclusion deviations include 1 patient was refractory to bortezomib, 1 patients progressed < 60 days after the last dose of bortezomib, 1 patient had no myeloma-related organ dysfunction at initial diagnosis, 1 patient's free light chain ratio was approved in error, 2 patients used antibiotics within 14 days of randomization, and 1 patient was randomized with grade 2 neuropathy. In the placebo arm, protocol violations regarding inclusion and exclusion criteria include 1 patient was refractory to bortezomib, 2 had minor laboratory deviations, 1 patient was allergic to thalidomide, 1 patient was refractory to bortezomib and 1 patient was on antibiotics at the cycle 1 day 1 visit. Regarding the protocol deviation of excluded medications, 1 patient in the placebo arm used ciprofloxacin. On the ixazomib arm, excluded medications that were used include ciprofloxacin, Ginkgo biloba, carbamazepine, clarithromycin and itraconazole.

Regarding protocol deviations associated with the ixazomib or placebo, percent compliance was calculated, by applicant, as $100\% \times (\text{study drug taken in mg}) / (\text{study drug expected to be taken in mg})$. Missed doses that made compliance $\leq 70\%$ were considered a major protocol deviation.

Table 5 Major Protocol Deviations

	Ixazomib + LenDex N=360 n (%)	Placebo + LenDex N=360 n (%)
Excluded Medication Taken	4	1
Inclusion/exclusion issue	7	6

	Ixazomib + LenDex N=360 n (%)	Placebo + LenDex N=360 n (%)
Major overdose error	1	0
compliance \leq 70% with ixazomib or placebo	7	8
Procedure/Assessment Not Done	0	1

Table of Demographic Characteristics

The demographics of the ITT population are displayed in Table 6. The mean age of the ITT population was 66 years of age with a minimum age of 30 and a maximum age of 91. Males were present slightly more than females at 56.6% of the ITT population. The majority of the ITT population was white at 84.6%. A total of 7.1% of the population was from the United States, and 13.3% was from North America. The countries of the ITT population are displayed in Table 7. As demonstrated in the table, the ITT population was global.

Table 6 Demographics of ITT population

	Ixazomib + LenDex (N=360) n (%)	Placebo + LenDex (N=362) n (%)	Total (N=722) n (%)
Sex			
Male	207 (57.5)	202 (56.1)	409 (56.6)
Female	153 (42.5)	160 (44.2)	313 (43.4)
Age			
Mean years (SD)	65.2	65.8	65.7
Median (years)	66	66	66
Min, max (years)	38, 91	30,89	30, 91
Age Group			
\geq 17 - < 65 years	148 (41.1)	157 (43.4)	305 (42.2)
\geq 65 years	212 (58.9)	205 (56.6)	417 (57.8)
> 65 - < 75 years	133 (36.9)	116 (32.0)	249 (34.5)
\geq 75 years	59 (16.4)	70 (19.3)	129 (17.9)
Race			
White	310 (86.1)	301 (83.1)	611 (84.6)
Black or African American	7 (1.9)	6 (1.7)	13 (1.8)
Asian	30 (8.3)	34 (9.4)	64 (8.9)
American Indian or Alaska Native	0 (0)	1 (0.3)	1 (0.1)
Native Hawaiian or Other Pacific Islander	2 (0.6)	2 (0.6)	4 (0.6)

	Ixazomib + LenDex (N=360) n (%)	Placebo + LenDex (N=362) n (%)	Total (N=722) n (%)
Other ¹	4 (1.1)	3 (0.8)	7 (1.0)
Not reported	7 (1.9)	15 (4.1)	22 (3.0)
Ethnicity			
Hispanic or Latino	9 (2.5)	12 (3.3)	21 (2.9)
Not Hispanic or Latino	339 (94.2)	333 (92.0)	672 (93.1)
Not reported	10 (2.8)	15 (4.1)	25 (3.5)
Missing	2 (0.6)	2 (0.6)	4 (0.6)
Region (optional)			
United States	28 (7.8)	23 (6.4)	51 (7.1)
Rest of the World			
Europe	247 (68.6)	236 (65.2)	483 (66.9)
North America	47 (13.1)	49 (13.5)	96 (13.3)
Asia Pacific	66 (18.3)	77 (21.3)	143 (19.8)

¹ Includes Arabic, Maori, New Zealand Maori, NZ European, White/New Zealand Maori and hospital not allowed to release private information

Table 7 Countries of ITT population

	Ixazomib +LenDex (n=360) N (%)	Placebo + LenDex (n=362) N (%)
Australia	9 (2.5)	8 (2.2)
Austria	5 (1.4)	4 (1.1)
Belgium	7 (2.0)	7 (2.0)
Canada	19 (5.3)	26 (7.2)
China	3 (0.8)	3 (0.8)
Czech Republic	15 (4.2)	21 (5.8)
Denmark	10 (2.8)	7 (2.0)
France	36 (10.0)	45 (12.4)
Germany	8 (2.2)	7 (2.0)
Hungry	18 (5.0)	21 (5.8)
Israel	19 (5.3)	14 (3.9)
Italy	24 (6.7)	15 (4.1)
Japan	20 (5.6)	21 (5.8)
Netherlands	3 (0.8)	6 (1.7)
New Zealand	28 (7.8)	39 (10.8)
Poland	21 (5.8)	20 (5.5)
Portugal	7 (2.0)	8 (2.5)
Romania	6 (1.7)	6 (1.7)

	Ixazomib +LenDex (n=360) N (%)	Placebo + LenDex (n=362) N (%)
Russian Federation	21 (5.8)	18 (5.0)
Singapore	2 (0.6)	4 (1.1)
South Korea	4 (1.1)	2 (0.6)
Spain	16 (4.4)	14 (3.9)
Sweden	15 (4.2)	12 (3.3)
Turkey	4 (1.1)	3 (0.8)
United Kingdom	12 (3.3)	8 (2.2)
United States	28 (7.8)	23 (6.4)

Other Baseline Characteristics

Other baseline characteristics are displayed in Table 8. The majority of the patients were relapsed with 11% having disease considered refractory. Patients considered high risk, based on cytogenetics were approximately 19%. Prior treatments of the ITT population are displayed in Table 9. As displayed in this table, approximately 60% had one prior line of therapy, approximately 55% had prior stem cell transplantation, approximately 45% were immune modulating agent naïve, and approximately 30% had not been exposed to a prior proteasome inhibitor.

Table 8 Baseline characteristics of the ITT population

	Ixazomib +LenDex N=360 N(%)	Placebo + LenDex N=362 N(%)	Total (N=722) N(%)
Baseline ECOG Performance Status			
0	180 (50.0)	170 (47.0)	350 (48.5)
1	156 (43.3)	164 (45.3)	320 (44.3)
2	18 (5.0)	24 (6.6)	42 (5.8)
Missing	6 (1.7)	4 (1.1)	10 (1.4)
Creatinine Clearance at Baseline			
Mean	83.0	81.7	
Median	78.4	78.4	
Minimum, Maximum	20.3, 232.8	26.6, 233.5	
Patients with bone marrow aspiration	357 (99.2)	358 (98.9)	715 (99.0)
Adequate for interpretation	345 (95.9)	336 (92.8)	681 (94.3)
Patients with bone marrow biopsy	10 (2.8)	24 (6.6)	34 (3.3)
Adequate for interpretation	9 (2.5)	22 (6.1)	31 (4.3)
% plasma cells in bone marrow			

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

	Ixazomib +LenDex N=360 N(%)	Placebo + LenDex N=362 N(%)	Total (N=722) N(%)
Mean	26.2	26.1	
Medium	18	20	
Minimum, Maximum	0, 100	0, 100	
Bone marrow cytogenetics collected	325 (90.3)	334 (92.3)	659 (91.3)
Conventional Karyotype	10 (2.8)	7 (1.9)	17 (2.4)
FISH	255 (70.8)	277 (76.5)	532 (73.7)
Both	49 (13.6)	35 (9.7)	84 (11.6)
Cytogenetics Abnormality Category			
Standard risk	199 (55.3)	216 (59.7)	415 (57.5)
High risk	75 (20.8)	62 (17.1)	137 (19.0)
Not available	86 (23.9)	84 (23.2)	170 (23.5)
Patient population			
Relapsed	276 (76.7)	280 (77.3)	556 (77.0)
Refractory	42 (11.7)	40 (11.0)	82 (11.4)
Refractory and relapsed	41 (11.4)	42 (11.6)	83 (11.5)
Best response to prior therapy			
CR	123 (34.2)	117 (32.3)	240 (33.2)
PR	198 (55.0)	210 (58.0)	408 (56.5)
SD	19 (5.3)	15 (4.1)	34 (4.7)
PD	8 (2.2)	11 (3.0)	19 (2.6)
Unable to assess	4 (1.1)	0	4 (0.6)
Unknown	7 (1.9)	9 (2.5)	16 (2.2)

Table 9 Prior treatments of ITT population

	Ixazomib +LenDex N=360 N(%)	Placebo + LenDex N=362 N(%)	Total (N=722) N(%)
Prior Lines of Therapy (stratification)			
1	212 (58.9)	213 (58.8)	425 (58.9)
2 or 3	148 (41.1)	149 (41.2)	297 (41.1)
Line of prior therapy (applicant review)			
1	224 (62.2)	217 (59.9)	441 (61.1)
2	97 (26.9)	111 (30.7)	208 (28.8)
3	3 (0.8)	34 (9.4)	37 (5.1)
Patients with stem cell transplant			
Autologous	212 (58.9)	199 (55.0)	411 (56.9)
	202 (56.1)	193 (53.3)	395 (54.7)

	Ixazomib +LenDex N=360 N(%)	Placebo + LenDex N=362 N(%)	Total (N=722) N(%)
Allogenic	6 (1.7)	4 (1.1)	10 (1.4)
Both	4 (1.1)	2 (0.6)	6 (0.8)
Prior IMiD			
Naïve	167 (46.4)	158 (43.6)	325 (45)
Exposed	193 (53.6)	204 (56.4)	397 (55.0)
Lenalidomide	36 (10.0)	34 (9.4)	70 (9.7)
Thalidomide	149 (41.4)	160 (44.2)	309 (42.8)
Lenamidomide and Thalidomide	8 (2.2)	10 (2.8)	18 (2.5)
Refractory to prior IMiD			
Yes	41 (11.4)	50 (13.8)	91 (12.6)
No	319 (88.6)	312 (86.2)	631 (87.4)
Prior Proteasome inhibitor			
Naïve	111 (30.8)	109 (30.1)	220 (30.5)
Exposed	249 (69.2)	253 (69.9)	502 (69.5)
Velcade	248 (68.9)	249 (68.8)	497 (68.8)
Carfilzomib	1 (0.3)	3 (0.8)	4 (0.6)
Both	0	1 (0.3)	1 (0.1)
Refractory to prior PI therapy			
Yes	22 (6.1)	17 (4.7)	39 (5.4)
No	338 (93.9)	345 (95.3)	683 (94.6)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance, based on the safety population, is displayed in Table 10. Percent compliance was calculated as $100\% \times (\text{study drug taken in mg}) / \text{study drug expected to be taken in mg}$. Compliance across the three drugs was similar between the two arms.

Table 10 Overall Treatment Compliance (%)

	Ixazomib + LenDex N=360	Placebo + LenDex N=360
Ixazomib/placebo		
Median	100	100
Mean	98.6	97.9
Minimum, Maximum	33.3, 300	50, 101.8
Dexamethasone		

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

	Ixazomib + LenDex N=360	Placebo + LenDex N=360
Median	100	100
Mean	96.7	96.9
Minimum, Maximum	25, 107.3	46.5, 113.3
Lenalidomide		
Median	100	100
Mean	98.9	98.7
Minimum, Maximum	14.3, 182.5	9.5, 159.7

Concomitant Medications

Concomitant medications, limited by patient for each therapeutic subgroup for the safety population, was analyzed and is displayed in Table 11. The relevant groups, based on reviewer assessment, are displayed. This evaluation is limited as it does not address the length of time the medication was used or the amount of different medications in each class.

Table 11 Concomitant Medications for the Safety Population

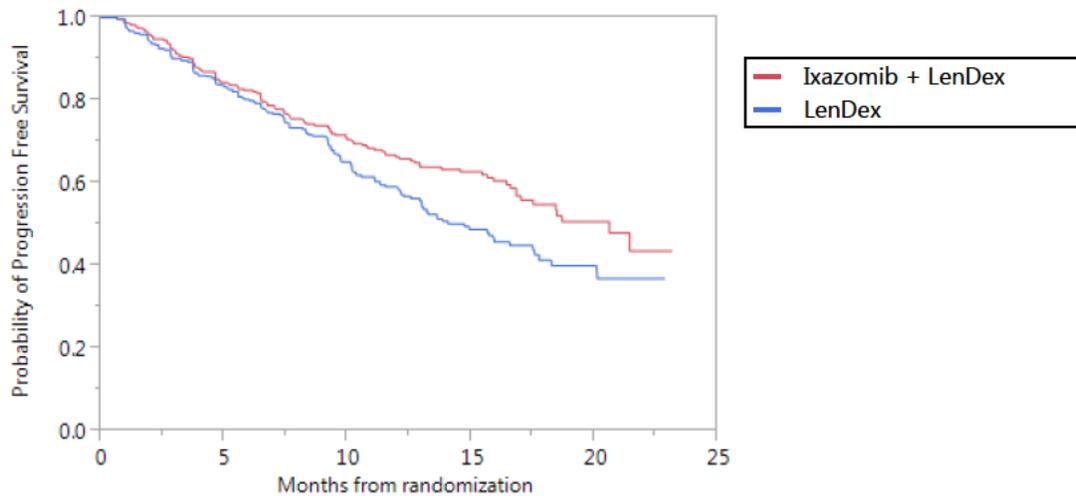
	Ixazomib + LenDex N=360 n (%)	Placebo + LenDex N=360 n (%)
Antithrombotic Agents	345 (95.8)	353 (98.1)
Analgesics	266 (73.9)	285 (79.2)
Antibacterials for systemic use	263 (73.1)	274 (76.1)
Antivirals for systemic use	231 (64.2)	216 (60.0)
Drugs for acid related disorders	272 (75.6)	264 (73.3)
Laxatives	130 (36.1)	119 (33.1)
Antidiarrheals, intestinal antiinflammatory	85 (23.6)	73 (20.3)
Antiemetics and antinauseants	68 (18.9)	43 (11.9)

Efficacy Results – Primary Endpoint

The primary endpoint was PFS, defined as the time from the date of randomization to the date of first documentation of disease progression based on central laboratory results and IMWG criteria evaluated by an IRC or death due to any cause, whichever was first.

The median PFS of the ITT population was 20.6 months in the Ixazomib + LenDex arm compared to 14.7 months in the placebo + LenDex arm (p value log-rank 0.016). A total of 129 patients in the Ixazomib + LenDex arm experienced progressive disease or death compared to 157 patients in the placebo + LenDex arm. The Kaplan-Meier plot is displayed in Figure 1. The hazard ratio was 0.74 (95% CI: 0.58, 0.93; p value = 0.011).

Figure 1 Kaplan-Meier Plot of PFS based on IRC assessment of ITT population



A total of 231 patients in the Ixazomib + LenDex arm were censored compared to 205 patients in the placebo + LenDex arm. The reason for censoring is displayed in Table 12.

Table 12 Reason for Censoring from IRC PFS assessment

	Ixazomib + LenDex	Placebo + LenDex
Total number censored	231	205
Reason for censoring		
No documented death or disease progression	196	161
Alternative therapies	18	25
Death or PD after more than 1 missed visit	3	8
Lost to follow up	2	0
No baseline/No post baseline	6	7
Withdrawal of consent	6	4

Updated Results

The final analysis of PFS, per IRC, was to be at the second interim analysis and was to occur when 365 PFS events occurred. The difference in median PFS observed was decreased from 5.9

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

months in the first analysis to 4.1 months with subsequent evaluation. Based on the Statistical Analysis Plan this was a non-inferential analysis, as the analysis of PFS at the first interim analysis met statistical significance. The results are displayed in Table 13.

Table 13 PFS results per IRC

	PFS (first interim analysis)		PFS updated results (non-inferential)	
	Ixazomib + LenDex	Placebo + LenDex	Ixazomib + LenDex	Placebo + LenDex
Events (%)	129 (35.8)	157 (43.4)	177 (47.6)	195 (52.4)
Progressed	114 (31.7)	145 (40.1)	158 (42.5)	180 (48.4)
Died	15 (4.2)	12 (3.3)	19 (5.1)	15 (4.0)
Median PFS (months) 95% CI	20.6 (17.0, NE)	14.7 (12.9, 17.6)	20.0 (18.0, 23.4)	15.9 (13.2, 18.8)
P value	0.013		0.0548	

Source: Statistical Review and Evaluation by Yun Wang, PhD

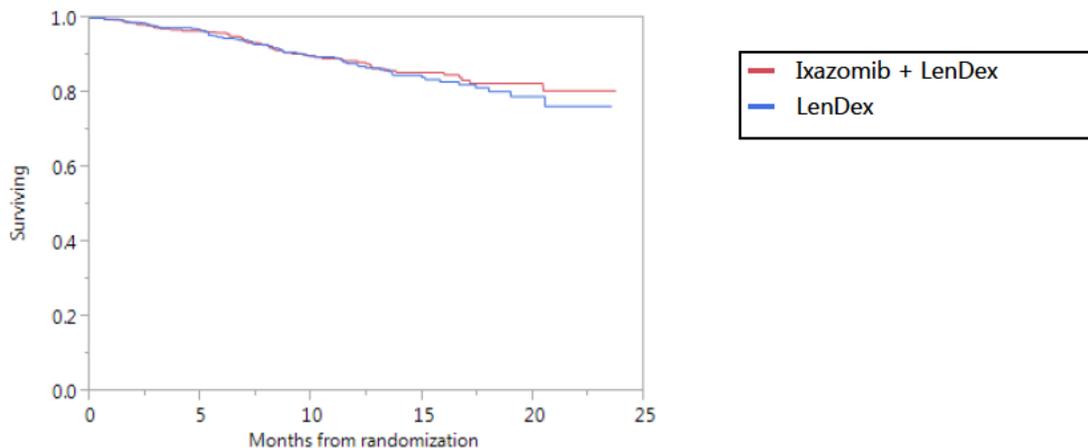
Data Quality and Integrity – Reviewers’ Assessment

The data quality and integrity were acceptable.

Efficacy Results – Secondary and other relevant endpoints

As the PFS was significant at the first analysis, the first key secondary endpoint overall survival was calculated. Overall survival was calculated using the date of randomization to the date of death from any cause. At the time of analysis, there were a total of 107 deaths, 51 in the Ixazomib + LenDex arm compared to 56 in the placebo + LenDex arm. The median OS was not reached in either treatment group (p value=0.606). The Kaplan-Meier plot is displayed in Figure 2.

Figure 2 Kaplan Meier Plot of Overall Survival of ITT population



Dose/Dose Response

Patients were started on the same dose of ixazomib.

Durability of Response

For durability of response, refer to the primary efficacy endpoint of PFS. The duration of response for responders in the ITT population is displayed in Table 14.

Table 14 Duration of Response

	Ixazomib + LenDex N=360	Placebo + LenDex N=362
Overall response rate, n(%)	282 (78.3)	259 (71.5)
Median duration of response, months	20.5	15.6
Number failed	93	104

Persistence of Effect

See previous analysis of progression free survival and duration of response.

Additional Analyses Conducted on the Individual Trial

The results of PFS for subgroups based on gender age, race and US are displayed in Table 15. Other subgroups are displayed in Table 16.

Reviewer Comment: The clinical applicability of the subgroups evaluated in Table 16, is unclear.

It is difficult to determine a clinically meaningful subgroup that can be associated with an increased benefit. For example, patients without a prior transplantation benefited more than patients with a transplantation, however, patients with 2 to 3 prior lines of therapy benefited more than patients with 1 prior line of therapy. These two facts seem to clinically contradict each other. Thus, further study may prove beneficial to find a particular population of multiple myeloma patients who will benefit the most from ixazomib.

Table 15 Hazard Ratio for PFS for subpopulations

	Hazard Ratio	Lower 95% CI, upper 95% CI
Sex		
Male (n=409)	0.749	0.547, 1.023
Female (n=313)	0.730	0.508, 1.041
Age		
<65 (n=305)	0.7396	0.5145, 1.0576
≥65 (n=417)	0.731	0.5344, 0.9981
Race		
White (n=617)	0.7429	0.5788, 0.9519
Asian (n=64)	0.7383	0.2462, 2.036
US compared to rest of world		
United States (n=51)	0.9248	0.3358, 2.5459
Rest of world (n=671)	0.7139	0.559, 0.9093

Table 16 Subgroups evaluation of First Interim Analysis of PFS per IRC

Subgroup	Ixazomib + LenDex		Placebo + LenDex		HR (95% CI)
	Event/N	Median (months)	Event/N	Median (months)	
Prior therapy					
1	80/212	20.6	88/213	16.6	0.88 (0.65, 1.20)
2 or 3	49/148	NE	69/149	12.9	0.58 (0.4, 0.84)
Prior stem cell transplant					
Yes	80/212	20.6	74/199	18.3	0.98 (0.71, 1.35)
No	49/148	18.5	83/163	12.2	0.54 (0.38, 0.78)
Creatinine clearance at baseline					
< 60 mL/min	37/79	16.4	44/100	14.9	1.03 (0.65, 1.64)
≥ 60 mL/min	92/281	21.4	113/261	14.1	0.65 (0.49, 0.87)

Source: Statistical Review and Evaluation by Yun Wang, PhD

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

A single clinical trial was relied on to demonstrate efficacy. The primary endpoint of this trial was PFS. PFS has been used to support approval in multiple myeloma. As discussed in section 2.2, PFS was used to support approval of bortezomib and carfilzomib, other currently approved proteasome inhibitors. PFS was also the basis for accelerated approval for panobinostat in 2015. In the pivotal trial for ixazomib, the combination arm of ixazomib, lenalidomide and dexamethasone improved progression free survival within the range of 4 to 6 months compared to the combination arm of placebo, lenalidomide and dexamethasone. The range is due to the abatement of progression free survival with continued follow up.

7.1.2. Secondary and Other Endpoints

The secondary endpoint of overall survival and overall survival in patients at high risk harboring del17 was not significant.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Patients enrolled to clinical trials tend to differ from the patient population exposed in the postmarketing setting. It is unclear based on the trial on the effectiveness of ixazomib in patients exposed to carfilzomib, another approved proteasome inhibitor, as only 1 patient on the ixazomib + LenDex arm was exposed to carfilzomib.

7.3. Integrated Assessment of Effectiveness

The efficacy of ixazomib was based on a single randomized, double-blind clinical trial in patients with multiple myeloma previously treated with 1 to 3 prior lines of therapy. The PFS improved, on average, of 4 to 6 months with the addition of ixazomib to lenalidomide and dexamethasone compared to placebo, lenalidomide and dexamethasone. An improvement in overall survival was not demonstrated.

8 Review of Safety

8.1. Safety Review Approach

Two routes of administration have been evaluated in ixazomib clinical development, oral and intravenous. Early phase 1 clinical studies were done with body surface area dosing. Per applicant, there was a lack of a relationship between body surface area and ixazomib clearance,

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

thus exposure following fixed dose should be independent of the body surface area. Following this, the development was switched to fixed dose during phase 1 trials.

The overall safety population consists of 15 trials, 990 patients. Not included in this population are the patients on the pivotal trial who did not receive ixazomib, patients in ongoing double-blind trials, investigator-initiated sponsored research studies, and patients who received IV ixazomib. Many of the studies which make up the analysis population were phase 1 dose-escalation studies which may include expansion or phase 2 cohorts, and studies with clinical pharmacology endpoints. As the pivotal trial was a randomized, double-blind, placebo control which allowed for better isolation of the effect of ixazomib, this trial served as the primary basis for the review.

The clinical review of safety was based on the safety population from trial C16010. This trial provided an adequate safety database which included a control arm leading to a better understanding of the effects of ixazomib. The safety population in trial C16010, was defined as all patients who received at least 1 dose of study drug. Patients were analyzed according to the treatment received, regardless of randomization.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Patients on the trial were to receive treatment until disease progression or unacceptable toxicity. The median number of treatment cycles received in the ixazomib arm was 13 (range 1-26) and 12 (range 1-25) in the placebo arm. The mean number of cycles received was 12.4 in the ixazomib arm compared to 12.1 in the placebo arm. The mean, median, minimum and maximum number of cycles received for the safety population by treatment arm for each drug is displayed in Table 17. The total dose administered of each drug by arm is displayed in Table 18. The safety database for ixazomib development is displayed in Table 19 and Table 20 displays the duration of exposure for ixazomib development.

Table 17 Exposure for each drug by treatment arm for safety population

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)		
	Ixazomib	Len	Dex	Placebo	Len	Dex
Mean	12.0	12.2	12.2	12.0	12.0	11.9
Median	12	13	13	12	12	12
Min, Max	1, 26	1, 26	1, 26	1, 25	1, 25	1, 25

Table 18 Total dose administered

	Ixazomib + LenDex	Placebo + LenDex
Ixazomib/Placebo		
Mean (mg)	136.0	138.5
Median (mg)	144.0	140.0
Min (mg), Max (mg)	4, 308	4, 300
Dexamethasone		
Mean (mg)	1648	1663.6
Median (mg)	1600	1608.0
Min (mg), Max (mg)	0, 4080	40, 4000
Lenalidomide		
Mean (mg)	5085.2	5147.3
Median (mg)	4817.5	4740
Min(mg), Max (mg)	0, 13350	20, 12925

Table 19 Safety Database for Ixazomib Development

Safety Database for Ixazomib Individuals exposed to the study drug in this development program N=990			
Clinical Trial Groups	Ixazomib (n= 990)	Active Control with placebo (n=360)	Placebo (n=0)
Normal Volunteers	0	0	0
Controlled trials conducted for this indication ¹	360	360	0
All other than controlled trials conducted for this indication	630 ²	N/A	0
Controlled trials conducted for other indications	N/A ³	N/A ³	0

1. to be used in product's labeling
2. All patients who received open-label treatment with ixazomib (either as a single agent or in combination with other chemotherapeutic regimens) for all indications included in the safety database (C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16011, C16013, C16015, C16017, C16018, C16020, and TB-MC010034).
3. Controlled trials for other indications are ongoing and remain blinded. Therefore, exposure by arm is not available for studies, C16014, C16019 and the C16010 China continuation.

Table 20 Duration of Exposure for Ixazomib Development

Number of patients exposed to the study drug = 990			
>=6 months	>=12 months	>=18 months	>=24 months or longer
N=483	N=241	N=105	N=32

8.2.2. Relevant characteristics of the safety population:

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

Aside from 4 patients, the characteristics of the safety population are the same as the ITT population. The characteristics of the ITT population are displayed in Table 8 and Table 9. Two patients in the ixazomib arm were not dosed with study treatment and are excluded from the safety population. One patient withdrew consent and another patient had a serious pretreatment AE. Two patients in the placebo arm were given ixazomib at some point during the treatment in error, and are included in the safety population of the ixazomib arm.

As displayed in Table 7, less than 10% of the patients in the trial were enrolled in the U.S. While the safety population is acceptable, there are areas where the trial population does not represent the intended target population. Over 80% of the patients on the trial were white, which does not represent the race of the intended population in the U.S. Limitations were placed on the patient population, as patients had to meet certain laboratory criteria in order to be enrolled as discussed in section 6.1.1. These criteria would include the majority of the U.S. multiple myeloma patients, but not all.

In the area of prior treatments the population may not be representative of the U.S. population. Approximately 45% of the population had not been exposed to an immune modulating agent and only 56.9% had a prior stem cell transplant. The majority of the patient population with multiple myeloma in the U.S. would likely receive an immune modulating agent, such as lenalidomide, in the front line setting.

8.2.3. Adequacy of the safety database:

The safety database is adequate with reference to the U.S. target population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity were identified. The submission was organized with appropriate analyses with detailed summaries when applicable. The applicant responded appropriately to requests for additional information.

8.3.2. Categorization of Adverse Events

Toxicity was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. Coding was done using MedDRA version 16.0.

8.3.3. Routine Clinical Tests

Routine hematology laboratory studies were done every two weeks for the first two cycles followed by once per cycle until the end of treatment. A cycle was defined as 28 days. Chemistry laboratory studies were done one per cycle until the end of treatment. Serum

chemistry consisted of basic chemistry laboratory studies, ALT, AST, alkaline phosphatase, total bilirubin, magnesium, calcium, phosphate, uric acid, and LDH. Hematology laboratory studies consisted of hemoglobin, hematocrit, platelet count and white count cell count with differential. A complete physical examination was done at the start and end of treatment. A symptom directed physical examination was done once per cycle. Adverse events were noted continuously from the first dose of study drug through 30 days after the last dose of study drug. Serious adverse events were noted from signing of informed consent through 30 days after the last dose of study drug. Skeletal related events and new primary malignancy were collected continuously from the start of study treatment until death or termination of the study. Narcotic and other analgesic use were recorded from the first dose of study drug until progression. The safety assessment methods and time points are adequate for the population and disease.

8.4. Safety Results

8.4.1. Deaths

There were a total of 29 deaths on the trial within 30 days of the last dose of study drug. There were 12 on study deaths in the ixazomib arm and 17 in the placebo arm.

Table 21 Narratives for patients who died on ixazomib arm within 30 days of study treatment

Cardiac arrest	07007-004 Patient was a 76-year-old man with MM with a history of MI, hypertension, coronary artery bypass graft, cardiac stent, hyperlipidemia, DVT who was hospitalized for sepsis during cycle 3, during which, he had two episodes of cardiac arrest, one of which was grade 5.
Cardiovascular insufficiency	22001-004 Patient was a 74-year-old man with one prior regimen with a history of BPH, low back pain and neurosurgical operation to remove a plasmacytoma. The patient received 13 cycles of protocol treatment and the patient died due to circulatory insufficiency at home. Autopsy performed, no report.
Aspiration pneumonia	29002-003 Patients was a 63-year-old man with DM, general weakness, neuropathy, dyspepsia with MM s/p two prior regimens and autologous stem cell transplantation. After cycle 7, the patient developed delirium and asthenia grade 3. An EEG showed moderate cerebral dysfunction. Treatment was stopped. Approximately one month later, he was diagnosed with hypoalbuminemia, which improved, and the following day he had aspiration pneumonia which lead to death.
Myocardial infarction	37006-010 Patient was a 60-year-old man with a history of neuropathy, MI, herpes zoster

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

	with MM s/p two prior regimens, autologous SCT. During cycle 10 the patient had an MI and died.
Coma	45001-005 Patient was a 78-year-old female with a history of atrial fibrillation, hypoacusia, chronic kidney disease with MM s/p two prior regimens who during cycle 4 had syncope and diarrhea. As a result of the diarrhea the patient discontinued treatment. Four days later she had a grade 3 CVA and grade 2 disseminated intravascular coagulation. Three days after that she had grade 3 acute cholecystitis, grade 3 pancreatitis and coma which lead to death.
Pulmonary embolism	51006-003 Patient was a 76-year-old man with a history of DVT with MM s/p two prior regimen who received six cycles of protocol treatment. The patient had a grade 4 PE, grade 4 cardio-respiratory arrest and grade 3 supraventricular tachycardia. Patient had received prophylactic antithrombotic therapy. The event led to the patient's death.
Multi-organ failure	52003-002 Patient was a 64-year-old man with a history of anemia with MM s/p one prior regimen and autologous SCT. Fourteen days after last dose the patient was hospitalized for gram negative sepsis and died from multi-organ failure.
Plasma cell myeloma	57001-003 Patient was an 84-year-old woman with a history of hypertension, CVA, PE, COPD with MM s/p prior therapy of cyclophosphamide. During cycle two the patient experienced grade 1 decreased renal clearance and the dose of lenalidomide was decreased. Four days later the patient had grade 4 decreased performance status and was admitted secondary to a fall. Study treatment was discontinued. Following this the patient experienced grade 2 acute renal failure, grade 3 respiratory tract infection, grade 4 thrombocytopenia, grade 3 leukopenia. One week after discontinuing protocol treatment the patient died from multiple myeloma.
Plasma cell myeloma	58003-003 Patient is a 54-year-old man with a history of hypertension, DM, gout, DVT with MM s/p autologous SCT. During cycle 2 the patient experienced progression of plasma cell myeloma and died.
Diastolic dysfunction	58003-008 Patient was a 60-year-old man with a history of atrial fibrillation, DVT, CHF, hypertension, renal failure with MM s/p one prior regimen and autologous SCT. The patient's protocol treatment was discontinued on cycle 1 day 15. One cycle 1 day 16 the patient had progressive SOB and lower extremity edema. He was diagnosed with grade 3 CHF which led to grade 4 cardiac arrest and grade 5 diastolic dysfunction.
Plasma cell	58018-001

myeloma	Patient was a 57-year-old man with a history of stage III chronic kidney disease, gout, hypertension, cardiomyopathy, COPD with MM s/ two prior regimens. One cycle 1 day 14 the patient was hospitalized for grade 3 acute renal failure with profound weakness, anorexia, and debility. The patient discontinued study due to acute renal failure. One day after hospitalization for acute renal failure the patient had grade 4 myocardial infarction and grade 2 hypotension. Four days later the patient had grade 5 plasma cell myeloma and was placed in palliative care.
Fungal pneumonia	58019-003 Patient was a 78-year-old female with hyperparathyroidism, CHF, hyperlipidemia, hypertension, venous thromboembolism. During cycle 10 the patient developed fungal pneumonia and neutropenia. Fungal pneumonia escalated to grade 5.

Table 22 Death Narratives within 30 days of last dose for Placebo arm

Cardiac failure	12001-003 Patient was a 73-year-old man with MM s/p three prior regimens and radiation, history of COPD, varicosity of lower extremities, HTN, steroid DM, who developed serious heart failure and died two days later.
Plasma cell myeloma	18003-002 Patient was a 68-year-old man with MM s/p three prior regimens, autologous SCT, with a history of dyslipidemia, HTN, right and left femoral popliteal thrombosis, and vertebral compression. He developed grade 4 plasma cell leukemia and died the same day.
Aspiration pneumonia	18005-007 Patient was a 79-year-old man with MM s/p 1 prior regimen with a history of BPH, functional colopathy, hypertension, arteriopathy of lower extremities, DM, hepatitis who developed 8 days after last dose developed grade 4 physical deterioration and seven days later aspiration pneumonia which led to his death.
Myocardial infarction	18009-006 Patient was a 74-year-old man with MM s/p 5 prior regimens, s/o two prior autologous transplantations. The patient had a MI and died the same day during cycle 6.
Sepsis	19007-001 Patient was a 69-year-old female with MM s/p autologous SCT with a history of osteoporosis, thoracic spine fracture, renal cell carcinoma, melanoma, arterial hypertension, who developed pneumonia and sepsis and died 4 days later.
Hypovolemic shock	28005-007 Patient was a 76-year-old female with MM with a history of atrial fibrillation, COPD, thyroidectomy, right femur fracture who developed increased bilirubin

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

	and hypovolemic shock that led to death.
Death	37001-016 Patient was an 84-year-old man with MM s/p two prior regimens, s/p radiation with a history of sciatica, gastritis, esophageal ulcer, and hyperlipidemia. The patient withdrew from study 14 days after last dose and died of unknown cause a week or so later. Autopsy was not performed.
Pulmonary embolism	37001-018 Patient is a 71-year-old man with MM s/p two prior regimens with a history of left femur fracture, compression fracture, compression fractures, bilateral knee replacements who developed a fatal PE during cycle 1.
Pneumococcal pneumonia	37002-013 Patient is a 76-year-old man with MM s/p 4 prior regimens, s/p autologous SCT with a history of atrial fibrillation, DVT, osteonecrosis of femoral heads and shoulders, hip replacement, shoulder replacement basal cell carcinoma who developed pneumococcal pneumonia during cycle 2 and died.
Cardiogenic shock	37003-002 Patient is a 67-year-old man with MM s/p one prior regimen and autologous SCT with history of NHL, neuropathy, dyslipidemia, gout, renal disease, DM, ischemic heart disease. The patient had three hospitalizations for atrial fibrillation. During cycle 6 the patient had a grade 3 acute MI and died from cardiogenic shock.
Cerebral hemorrhage	37004-009 Patient was a 70-year-old female with MM s/p two prior regimens, autologous SCT, radiation, with a history of atrial fibrillation, breast cancer, PE, renal insufficiency, SOB with exertion, who developed grade 3 epistaxis requiring platelet and RBC transfusion during cycle 12. Approximately two weeks later the patient was found unresponsive from possible intracerebral hemorrhage. Two days later the patient died.
Plasma cell myeloma	42001-004 Patient was a 48-year-old male with MM s/p one prior regimen and dexamethasone with a history of gastric ulcer, renal failure and COPD who received two cycles of protocol treatment. Seventeen days after protocol treatment the patient developed progressive disease, was treated with bortezomib and dexamethasone. Nine days after starting this therapy the patient died from progressive disease.
Aortic dissection	45003-002 Patient is a 76-year-old male with MM s/p three prior regimens with a history of duodenal ulcer, bronchitis, ischemic heart disease, abdominal aortic aneurysm, hypertension, paroxysmal atrial fibrillation, dyslipidemia who received 5 cycles of protocol treatment. Eleven days after last dose the patients was hospitalized for abdominal aortic dissection and died the next day.
Cellulitis	45003-005

	Patient was a 62-year-old man with MM with a history of hypertension, ischemic cardiac disease, right leg post-thrombotic syndrome, chronic renal disease and lumbar plasmacytoma who received three cycles of protocol treatment and developed grade 2 cellulitis (phlegmon buttock) and died two days later.
Suicide	46005-003 Patient was a 56-year-old man with MM s/p three prior regimens, two autologous SCT with a history of arterial hypertension, DM, pulmonary aspergillosis who committed suicide. The patient had no history of depression or suicidal thoughts. The motive is unknown.
Plasma cell myeloma	46006-002 Patient was a 61-year-old female with MM s/p two prior regimens with a history of DM, hypertonic disease, and chronic pyelonephritis who received 8 cycles of protocol treatment. On C9D1 visit the patient had laboratory studies consistent with progressive disease. Patient died 13 days later.
Cardiac failure	46008-008 Patient was a 48-year-old man with MM s/p two prior regimens with a history of thyroid hyperplasia, COPD, cardiac arteriosclerosis who received 15 cycles of protocol treatment. The patient developed grade 5 acute cardiac failure and grade 2 disseminated intravascular coagulation.

Reviewer Comments: Overall, there were fewer deaths, until 30 days after last dose of study drug, on the ixazomib arm. Death from progressive disease and infection was balanced between the two arms, with 3 on each arm. Ixazomib, did not appear to be associated with an increased risk of death from cardiac disease. Based on reviewer analysis, there were two deaths from cardiac disease on the ixazomib arm and 4 on the placebo arm.

8.4.2. Serious Adverse Events

A total of 144 patients (40%) on the ixazomib + LenDex arm had at least one serious adverse event compared to 161 patients (44.8%) of patients on the placebo + LenDex arm. The serious adverse events that occurred in more than 2% of all patients overall are pneumonia (6.5% of all patients) and pyrexia (3.3% of patients). Table 23 displays serious adverse events which occurred in more than 1% of patients overall.

Table 23 Serious Adverse Events

	Ixazomib + LenDex				Placebo + LenDex			
	Grades 1, 2		Grades 3, 4, 5		Grade 1, 2		Grade 3, 4, 5	
	n	%	n	%	n	%	n	%
Pneumonia	1	0.3	19	5.3	1	0.3	26	7.2
Pyrexia	7	1.9	3	0.8	10	2.8	4	1.1
Pulmonary embolism	0	0	6	1.7	0	0	8	2.2

	Ixazomib + LenDex				Placebo + LenDex			
	Grades 1, 2		Grades 3, 4, 5		Grade 1, 2		Grade 3, 4, 5	
	n	%	n	%	n	%	n	%
Plasma cell myeloma	0	0	5	1.4	0	0	8	2.2
Anemia	2	0.6	1	0.3	2	0.6	6	1.7
Atrial fibrillation	1	0.3	4	1.1	3	0.8	3	0.8
Febrile neutropenia	0	0	2	0.6	0	0	7	1.9
Thrombocytopenia	0	0	4	1.1	0	0	5	1.4
Diarrhea	0	0	7	1.9	2	0.6	0	0
Acute renal failure	1	0.3	4	1.1	0	0	4	1.1
Deep vein thrombosis	3	0.8	1	0.3	3	0.8	2	0.6
Bronchitis	1	0.3	0	0	1	0.3	6	1.7

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

A total of 51 patients (14.2%) on the ixazomib + LenDex arm discontinued from the trial secondary to a TEAE (treatment emergent adverse event) compared to 45 patients (12.5%) on the placebo + LenDex arm. Table 24 displays the TEAE which led to discontinuation from the trial that occurred in more than 3 patients overall. In Table 24 the TEAE that were more common on the ixazomib + LenDex arm are diarrhea, fatigue, asthenia, peripheral sensory neuropathy and septic shock.

Table 24 TEAE which resulted in discontinuation from the trial in the safety population

	Ixazomib + LenDex (N=360)		Placebo + LenDex (N=360)	
	n	%	n	%
Blood and lymphatic system disorders				
Thrombocytopenia	2	0.6	3	0.8
Anemia	1	0.3	2	0.6
Cardiac Disorders				
Cardiac failures	0	0	3	0.8
General disorders and administration site conditions				
Fatigue	3	0.8	1	0.3
Pyrexia	2	0.6	2	0.6
Asthenia	3	0.8	0	0
General physical health deterioration	1	0.3	2	0.6
Infections and Infestations				
Pneumonia	1	0.3	3	0.8
Septic Shock	2	0.6	1	0.3
Neoplasms benign, malignant and unspecified				

	Ixazomib + LenDex (N=360)		Placebo + LenDex (N=360)	
	n	%	n	%
Plasma cell myeloma	1	0.3	4	1.1
Nervous System Disorders				
Peripheral Sensory Neuropathy	2	0.6	1	0.3

A total of 54 patients (15%) discontinued ixazomib as a result of a TEAE event compared to 49 (13.6%) patients on the placebo + LenDex arm discontinuing placebo as a result of a treatment emergent adverse event. The TEAE which led to discontinuation of ixazomib, as compared to placebo, that were more common in the ixazomib arm by 1% are diarrhea and fatigue.

A total of 217 patients (60.3%) delayed, held, reduced or discontinued ixazomib as a result of a treatment emergent adverse event compared to 178 patients (49.4%) delaying, holding, reducing, or discontinuing placebo as a result of an adverse event. The TEAE which led to discontinuation, holding, reducing, or delaying ixazomib or placebo that occurred in more than 4% of the population overall in decreasing incidence are displayed in Table 25. The TEAE that were more common in the ixazomib arm in Table 25 are thrombocytopenia, diarrhea, and peripheral sensory neuropathy.

Table 25 TEAE which led to discontinuation, reduction, holding or delaying ixazomib or placebo

	Ixazomib + LenDex		Placebo + LenDex	
	n	%	n	%
Neutropenia	49	13.6	49	13.6
Thrombocytopenia	31	8.6	20	5.6
Diarrhea	30	8.3	10	2.8
Pneumonia	14	3.9	16	4.4
Peripheral sensory neuropathy	20	5.6	9	2.5

Table derived from ADAE analysis dataset using AEACMLN2 flag

Dose Reductions due to Adverse Events

Ixazomib and lenalidomide have overlapping toxicities. The protocol specifically addressed the adjustment of study medication or lenalidomide due to the toxicities of thrombocytopenia, neutropenia and rash as these toxicities were felt to be overlapping. These three toxicities and dose adjustments associated with them are discussed in further detail below.

Thrombocytopenia

The protocol used a value of $>30,000/\text{mm}^3$, such that, no dose adjustment was to be done until the platelet count fell below this value. According to the protocol once the platelet count fell below $30,000/\text{mm}^3$, treatment was to be interrupted and the complete blood count was to be

followed weekly. For the first decrease below 30,000/mm³, lenalidomide was to be resumed at the next lower dose level and the dose of ixazomib was to be maintained after the platelet count returned to $\geq 30,000/\text{mm}^3$. For the second fall below this threshold, the already reduced dose of lenalidomide was to be maintained, and the dose of ixazomib was to be reduced when the platelet count improved to $\geq 30,000/\text{mm}^3$. Holding both medications and then alternating dose reduction of the two medications was continued such that the 5th fall to $< 30,000/\text{mm}^3$ results in reduction of lenalidomide. The dose of lenalidomide should not be reduced to less than 5 mg and the dose of ixazomib should not be reduced to less than 2.3 mg.

To determine if the rules summarized above were followed in general, the adverse events of thrombocytopenia and platelet count decrease were analyzed. For any patient who had a dose modification or discontinuation of ixazomib as a result of thrombocytopenia or platelet count decrease, the lowest grade at which a dose adjustment was made is displayed in Table 26.

As displayed in Table 26, 15 patients had an adjustment to the ixazomib dose for grade 2 thrombocytopenia and 1 patient for grade 1 thrombocytopenia. According to the protocol, no patient should have had a dose modification for grade 1 or grade 2 thrombocytopenia. As this number of patients is small, it is difficult to determine the effect of efficacy this had. As the parameter for grade 3 thrombocytopenia is 25,000-50,000/mm³, it is expected that some patients would have an ixazomib dose adjusted for grade 3 thrombocytopenia as the protocol had a threshold of $< 30,000/\text{mm}^3$ for platelet count dose adjustments.

Table 26 Lowest grade of thrombocytopenia which resulted in dose modification

	Grade 1	Grade 2	Grade 3	Grade 4
Ixazomib + LenDex	1 patient	15 patients	12 patients	8 patients
Placebo + LenDex	1 patient	12 patients	7 patients	4 patients

Analysis done using AEACMLN2 dose adjustment flag in ADAE dataset

Rash

For rash, similar to thrombocytopenia, the protocol had specific dose modification instructions in place as this was considered to be an overlapping toxicity between ixazomib and lenalidomide. For the first occurrence of grade 2 or 3 rash, ixazomib was to be continued and lenalidomide was to be interrupted and resumed one dose level lower if the rash improved to $<$ grade 2 in the same cycle. For the second occurrence, if it was grade 2 rash, both drugs were to be held, and if the rash improved to $<$ grade 2 within the same cycle, both drugs would be resumed and the dose maintained for both drugs. If the second occurrence was grade 3 rash, both drugs would be held, and ixazomib was to be reduced one dose level and lenalidomide should have been maintained at the same dose level if the rash improved to $<$ grade 2 within the same cycle. For the third occurrence of grade 2 or 3 rash, again treatment is interrupted for both drugs and if the rash improved to $<$ grade 2 with the same cycle the dose of ixazomib should have been maintained and lenalidomide should have been resumed at the next lower dose. For the fourth occurrence of grade 2 rash, again both drugs are interrupted and both

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

restarted at the same dose level, if the rash improves to <grade 2 within same cycle. For the fourth occurrence, if it is grade 3, the same requirements apply for dose interruption and resumption, however, ixazomib was to be dose reduced one dose level. For the fifth occurrence, for grade 2 or 3, again the interruption and restarting rules apply, but only lenalidomide was to be dose reduced one dose level.

For patients who had a dose held, reduced or delayed secondary to an adverse event in the HLT of rashes, eruptions and exanthems, NEC, the minimum grade for which a dose adjustment of ixazomib occurred is displayed in Table 27. This analysis is limited to the minimum grade an adjustment occurred per patient. As displayed in Table 27, not many patients had dose adjustments of ixazomib for rash. Two patients overall had a dose adjustment for grade 1 rash, which per protocol, should not have occurred.

Table 27 Dose adjustment secondary to rash

	Grade 1	Grade 2	Grade 3
Ixazomib + LenDex	1 patient	5 patients	5 patients
Placebo + LenDex	1 patient	1 patient	2 patients

Analysis done using AEACMLN2 dose adjustment flag in ADAE dataset

Neutropenia

For neutropenia, similar to rash and thrombocytopenia, the protocol had dose modification guidelines as this was considered to be an overlapping toxicity between ixazomib and lenalidomide. The dose adjustments were alternating between ixazomib and lenalidomide. For the first fall to $<0.5 \times 10^9/L$, both drugs were to be held and resumed if the neutropenia returned to $\geq 500 \times 10^9/L$ within the same cycle, lenalidomide was to be dose reduced to the next lower dose level. For the second fall, again both drugs are held and restarted at the same values mentioned above, however, ixazomib was to be resumed at the next lower dose and lenalidomide was maintained at the same dose. This pattern of alternating the drug being dose reduced is continued until the fifth fall when lenalidomide is dose reduced.

The number of patients who had a dose reduction of ixazomib or placebo secondary to neutropenia or neutrophil count decreased is displayed in Table 28. This calculation was done using the preferred terms of neutropenia and neutrophil count decreased limiting the analysis to the minimum grade when a dose reduction was done for each patient. As displayed in Table 28, a small number of patients did undergo dose reduction of ixazomib for <grade 4 neutropenia, which was not per protocol.

Table 28 Dose Reductions secondary to neutropenia

	Grade 1	Grade 2	Grade 3	Grade 4
Ixazomib + LenDex	0	1	7	4
Placebo + LenDex	1	1	1	7

8.4.4. Significant Adverse Events

NCI CTCAE Grade 3, 4 and 5 TEAE are displayed in Table 29. The more common grade 3, 4 and 5 adverse events in the ixazomib + LenDex arm where the difference between the arms is $\geq 5\%$, are thrombocytopenia (13%) and diarrhea (6%).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAE where the difference in overall incidence between the two arms is greater than 5% is displayed in Table 29. The TEAE are limited to the maximum grade for each patient, for each adverse event. Vomiting, thrombocytopenia, constipation, peripheral edema, diarrhea, rash maculo-papular and nausea were more common in the ixazomib + LenDex arm, where insomnia, pyrexia and muscle spasms were more common in the Placebo + LenDex arm.

Table 29 TEAE where difference in incidence between two arms $\geq 5\%$

	Ixazomib + LenDex (N=360)				Placebo + LenDex (N=360)			
	All grades		Grade 3, 4, 5		All grades		Grade 3, 4, 5	
	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Thrombocytopenia	73	20.3	48	13.3	36	10	19	5.3
Gastrointestinal disorders								
Vomiting	79	21.9	4	1.1	39	10.8	2	0.6
Constipation	122	33.9	1	0.3	90	25	1	0.3
Diarrhea	151	41.9	22	6.1	130	36.1	8	2.2
Nausea	92	25.6	6	1.7	74	20.6	0	0
General and Administrative Site Conditions								
Peripheral edema	91	25.3	8	2.2	66	18.3	4	1.1
Pyrexia	46	12.8	3	0.8	69	19.2	5	1.4
Musculoskeletal and connective tissue disorders								
Muscle Spams	63	17.5	0	0	91	25.3	2	0.6
Psychiatric disorders								
Insomnia	70	19.4	7	1.9	90	25	9	2.5
Skin and subcutaneous tissue disorders								
Rash maculo-papular	32	8.9	8	2.2	12	3.3	2	0.6

8.4.6. Laboratory Findings

The worst on trial grade each patient developed for individual laboratory tests in displayed Table 30. The laboratory tests were the difference in incidence of all grades of abnormal laboratory test between the ixazomib + LenDex arm and the placebo + LenDex are was greater than 5% are thrombocytopenia and hypernatremia. The laboratory tests were the difference in incidence of grade 3 and grade 4 was >5% between the two arms was thrombocytopenia, lymphopenia and leukopenia.

Table 30 Laboratory tests

	Ixazomib + LenDex (N=360)				Placebo + LenDex (N=360)			
	All grades		Grade 3, 4		All grades		Grade 3, 4	
	n	%	n	%	n	%	n	%
Liver Function Tests								
ALT	77	21.4	5	1.4	84	23.3	4	1.1
AST	50	13.9	2	0.6	53	14.7	4	1.1
Alkaline Phosphatase	48	13.3	0	0	39	10.8	0	0
Hyperbilirubinemia	30	8.3	4	1.1	34	9.4	4	1.1
Chemistry								
Hypercalcemia	12	3.3	7	1.9	13	3.6	4	1.1
Increased creatinine	82	22.8	6	1.7	82	22.8	7	1.9
Hyperglycemia	221	58.6	8	2.2	206	57.2	21	5.8
Hypoalbuminemia	99	27.5	5	1.4	102	28.3	5	1.4
Hypocalcemia	140	38.9	16	4.4	142	39.3	19	5.3
Hypoglycemia	21	5.8	4	1.1	19	5.3	3	0.8
Hypomagnesium	43	11.9	0	0	58	16.1	5	1.4
Hypophosphatemia	139	38.6	35	9.7	146	40.6	21	5.8
Hypokalemia	72	20	16	4.4	79	21.9	8	2.2
Hyponatremia	55	15.3	9	2.5	44	12.2	13	3.6
Hypernatremia	116	32.2	0	0	97	26.9	0	0
Hematology								
Low hemoglobin	222	61.7	42	11.7	230	63.9	46	12.8
Thrombocytopenia	281	78.1	91	25.3	197	54.7	37	10.3
Leukopenia	268	74.4	71	19.7	265	73.6	52	14.4
Lymphopenia	217	60.3	117	32.5	212	58.9	85	23.6
Neutropenia	227	63.1	79	21.9	232	64.4	97	26.9

Platelet count

Based on the protocol, hematology laboratory studies were initially done every two weeks for the first three cycles and then every cycle for the remainder of the cycles. The average platelet

count for each arm for the first 4 cycles is displayed in Figure 3. Figure 4 displays the average platelet count on day 1 of each cycle. A total of 11 patients (3.1%) on the Ixazomib + LenDex arm and 5 patients (1.4%) on the placebo + LenDex arm developed a platelet count $\leq 10,000/\text{mm}^3$. A total of 2 patients (0.6%) on the ixazomib + LenDex arm and 1 patient (0.3%) on the LenDex arm developed a platelet count of $\leq 5,000/\text{mm}^3$.

Figure 3 Average platelet count per visit

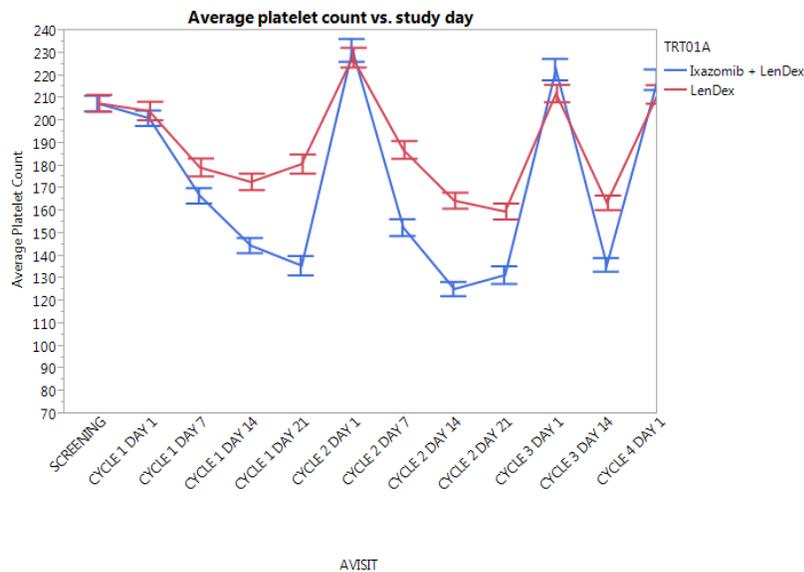
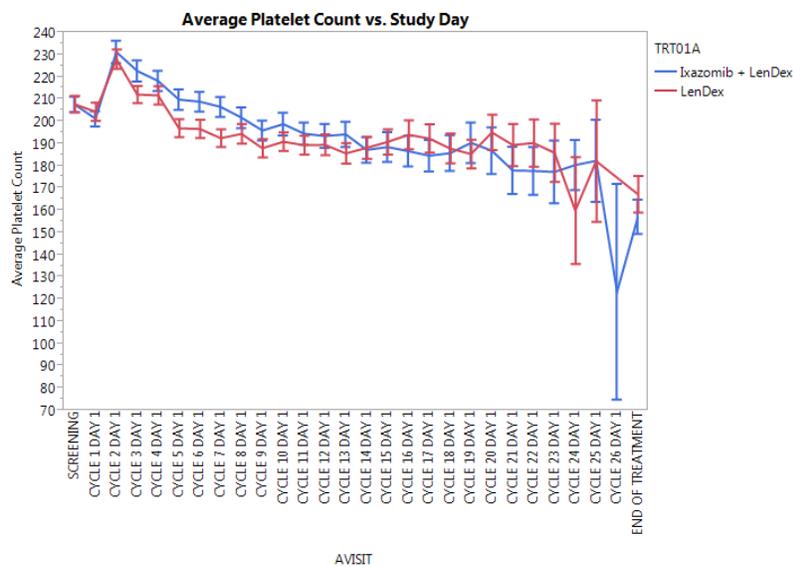


Figure 4 Average platelet count on the first day of each cycle



8.4.7. Vital Signs

An analysis of vital signs was not conducted. Any clinically significant changes in vital signs should be captured as adverse events.

8.4.8. Electrocardiograms (ECGs)

A total of 14 patients on the ixazomib + LenDex arm and 12 patients on the placebo + LenDex developed ECGs considered abnormal, clinically significant, after screening. On the ixazomib arm these ECG abnormalities included atrial flutter, tachycardiac atrial fibrillation, sinus bradycardia, tachycardia, atrial fibrillation with aberrant conduction, possible ischemia, occasional ventricular premature complexes, QTC > 500 ms, atrial fibrillation, atrial fibrillation with rapid ventricular response, sinus brady with possible left atrial enlargement, and left ventricular hypertrophy with first degree atrioventricular block. On the placebo arm these ECG abnormalities include atrial fibrillation (4 patients), atrioventricular block, diffuse ST-T wave abnormalities, left bundle branch block pacemaker, atrial fibrillation with rapid ventricular response with ST and T wave abnormalities, sinus tachycardia with right bundle branch block, sinus arrhythmia with ST and T wave abnormalities, and atrial fibrillation rate controlled.

8.4.9. QT

The Interdisciplinary Review Team for QT Studies was consulted and reviewed four open-label dose escalation studies. The consult findings are below:

This PK-QTc analysis was conducted to evaluate the effect of MLN2238 on QT interval prolongation. Drug concentrations in these studies covered the anticipated therapeutic range. No clear dose-response and exposure-response for QTc were observed.

8.4.10. Immunogenicity

Assessments for immunogenicity are generally not needed for small molecule drugs.

8.5. Analysis of Submission-Specific Safety Issues

In section 8.4.5 TEAE are discussed. In section 8.4.5 no reclassification or grouping by the reviewer was done. TEAEs where the difference in overall incidence is greater than 5% and occurred more frequently in the ixazomib + LenDex arm, as discussed in section 8.4.5, are vomiting, thrombocytopenia, constipation, peripheral edema diarrhea, rash and nausea.

8.5.1. Thrombocytopenia

Thrombocytopenia was a significant adverse event with a difference in overall incidence between the two arms of 10.3%. On the ixazomib + LenDex arm, 20.3% of patients had a least

one episode of thrombocytopenia compared to 10% on the placebo + LenDex arm. The incidence increases if a broad SMQ of hematopoietic thrombocytopenia is used as displayed in Table 31. This SMQ includes the preferred terms thrombocytopenia and platelet count decreased.

Table 31 Broad SMQ for Hematopoietic thrombocytopenia

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Hematopoietic thrombocytopenia	216	99	27.5	97	50	14.0	13.6

8.5.2. Gastrointestinal

Gastrointestinal TEAE are a concern with ixazomib. Four of the seven preferred terms, with a difference an overall incidence > 5% overall incidence, which are more common in the Ixazomib + LenDex arm are gastrointestinal related. These preferred terms are vomiting, constipation, diarrhea and nausea. Using a MAED SMQ analysis, a broad SMQ of gastrointestinal nonspecific inflammation and dysfunction conditions, was associated with a risk difference of 8.33. A broad SMQ of acute pancreatitis is associated with risk difference of 10.8. This is displayed in Table 32. The preferred terms included in the SMQ analysis are displayed in Table 33.

Table 32 SMQ analysis for GI adverse events

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Gastrointestinal nonspecific inflammation and dysfunctional conditions							
Broad	920	255	70.8	619	225	62.5	8.3
Narrow	901	253	70.3	605	224	62.2	8.1
Acute Pancreatitis							
Broad	357	153	42.5	209	114	31.7	10.8
Narrow	1	1	0.3	0	0	0	0.3

Table 33 Preferred Terms in SMQ

Gastrointestinal nonspecific inflammation and dysfunctional conditions		Pancreatitis	
Narrow	Broad (+ narrow)	Narrow	Broad (+ narrow)
Abdominal discomfort	Chest pain	Pancreatitis	Abdominal distension

Gastrointestinal nonspecific inflammation and dysfunctional conditions		Pancreatitis	
Narrow	Broad (+ narrow)	Narrow	Broad (+ narrow)
Abdominal distension	Diverticulitis		Abdominal pain
Abdominal pain	Diverticulum intestinal		Abdominal pain upper
Abdominal pain lower	Dysphagia		Abdominal rigidity
Abdominal pain upper	Gastric dilatation		Abdominal tenderness
Abdominal tenderness	Gastrointestinal motility disorder		Amylase increased
Abnormal faeces	Hypovolaemia		Blood bilirubin increased
Bowel movement irregularity	Esophageal achalasia		Gastrointestinal pain
Constipation	Pancreatic insufficiency		Hyperbilirubinemia
Diarrhea			Ileus paralytic
Epigastric discomfort			Nausea
Eructation			Vomiting
Flatulence			
Gastritis			
Gastroduodenitis			
Gastrointestinal pain			
Gastroesophageal reflux disease			
Nausea			
Non-cardiac chest pain			
Vomiting			

8.5.3. Cutaneous reactions

Rash is an adverse event of concern based on analysis of TEAE. Using an SMQ analysis of severe cutaneous adverse reactions a risk difference of 8.6 was observed for a broad SMQ and 1.9 risk difference for a narrow SMQ. The risk difference for the broad and narrow is displayed in Table 34 and the preferred terms included are displayed in Table 35.

Table 34 SMQ analysis

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Severe cutaneous adverse reactions							
Broad	67	54	15	26	23	6.4	8.6
Narrow	10	8	2.2	1	1	0.3	1.9

Table 35 Preferred terms in SMQ

Severe cutaneous adverse reactions	
Narrow	Broad (+ narrow)
Cutaneous vasculitis	Blister
Dermatitis bullous	Conjunctivitis
Dermatitis exfoliative	Drug eruption
Erythema multiforme	Mouth ulceration
Toxic skin eruption	Oral mucosal blistering
	Skin erosion
	Skin exfoliation
	stomatitis

8.5.4. Peripheral Neuropathy

For peripheral neuropathy, a closely related preferred term to peripheral neuropathy did not meet the criteria of a difference in incidence of greater than 5% between the two arms. The four preferred terms with a difference in incidence greater than 2% in the organ class of nervous system disorders are displayed in Table 36.

Table 36 TEAE in Nervous System Disorders with a difference in incidence of $\geq 2\%$

	Ixazomib + LenDex (N=360)				Placebo + LenDex (N=360)			
	All grades		Grade 3, 4, 5		All grades		Grade 3, 4, 5	
	n	%	n	%	n	%	n	%
Peripheral sensory neuropathy	67	18.6	5	1.4	50	13.9	3	0.8
Dizziness	48	13.3	2	0.6	34	9.4	1	0.3
Paraesthesia	28	7.8	1	0.3	14	3.9	0	0
Neuropathy peripheral	37	10.3	1	0.3	29	8.1	3	0.8

Using a SMQ analysis, an increase in the safety signal for peripheral neuropathy is noted. The SMQ peripheral neuropathy risk difference for broad and narrow analysis is displayed in Table

37. The adverse event terms included in this analysis are displayed in Table 38. Using an SMQ analysis, peripheral neuropathy is a concern.

Table 37 SMQ analysis for peripheral neuropathy

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Broad	239	140	38.9	167	112	31.1	7.8
Narrow	160	109	30.3	106	81	22.5	7.8

Table 38 TEAE included in Peripheral Neuropathy SMQ

Peripheral Neuropathy	
Narrow	Broad (+ narrow)
Acute polyneuropathy	Burning sensation
Neuralgia	Dysaesthesia
Neuritis	Formication
Neuropathy peripheral	Gait disturbance
Peripheral motor neuropathy	Hypoaesthesia
Peripheral sensorimotor neuropathy	Hyporeflexia
Peripheral sensory neuropathy	Muscle atrophy
Polyneuropathy	Muscular weakness
Sensory disturbance	Paraesthesia
	Peroneal nerve palsy

8.5.5. Cardiac toxicities

Cardiac toxicities are not noted to be an adverse event of concern based on preferred term analysis done in section 8.4.5. Cardiac toxicity is a concern with other drugs with the same mechanism of action. Cardiac related broad SMQ analyses with a risk difference over 5 are cardiac failure, and hemodynamic edema, effusions and fluid overload. The broad SMQ of cardiac arrhythmia is not a significant safety signal with a risk difference of 0.6. The more specific level 2 cardiac arrhythmia SMQ analysis of arrhythmia related investigations, signs and symptoms is a possible safety signal with a risk difference of 2.2. These SMQs are displayed in Table 39.

Table 39 Broad SMQs cardiac related

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Cardiac failure	146	98	27.2	104	75	20.8	6.4

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Cardiac arrhythmias	68	47	13.1	58	45	12.5	0.6
Arrhythmia related investigations, signs and symptoms (level 2)	34	28	7.8	24	20	5.6	2.2
Haemodynamic edema, effusions and fluid overload	146	101	28.1	99	71	19.7	8.3

The overwhelming majority of events in the cardiac failure SMQ are peripheral edema. There are 250 events in the cardiac failure SMQ and 214 (85.6%) of these are peripheral edema. If the preferred term of peripheral edema and edema is removed there are 13 patients who had at least one event of the remaining preferred terms on the Ixazomib + LenDex arm compared to 11 on the placebo + LenDex arm.

The situation is similar for the hemodynamic edema, effusions and fluid overload broad SMQ analysis. This SMQ consists of 245 events, again 214 of these or 87.3% are peripheral edema. If the preferred term of peripheral edema is removed the proportion of patients experiencing a preferred term in this SMQ is 4.2% (15 patients) in the Ixazomib + LenDex arm compared to 3.3% (12 patients) in the Placebo + LenDex arm.

In conclusion, the cardiac failure signal appears to be related to peripheral edema. The SMQ of arrhythmia related investigations, signs and symptoms, with a risk difference of 2.2, includes the preferred terms of bradycardia, cardiac arrest, cardio-respiratory arrest, palpitations, syncope and tachycardia. In conclusion routine monitoring is recommended in the post-marketing setting.

8.5.6. Pulmonary toxicity

Similar to cardiac toxicity, pulmonary toxicity is not a concern based on the analysis done on TEAE in section 8.4.5. However, pulmonary toxicity including respiratory distress, pulmonary hypertension and dyspnea are adverse events of interest in drugs with the same mechanism of action. Using broad SMQ analysis for pulmonary toxicity, no significant safety signal is demonstrated. Broad SMQs for pulmonary toxicities are displayed in Table 40. In Table 41, the preferred terms for the SMQ of pulmonary hypertension are displayed. As noted in this table on the Ixazomib + LenDex arm, one patient developed pulmonary hypertension and one developed pulmonary microemboli. This is noted, but not a strong safety signal for pulmonary toxicity.

Table 40 Broad SMQ for pulmonary toxicity

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Asthma/ bronchospasm	2	2	0.6	6	6	1.7	-1.1
Interstitial lung disease	3	3	0.8	3	3	0.8	0
Pulmonary hypertension	52	43	11.9	63	52	14.4	-2.5
Eosinophilic pneumonia	61	49	13.6	69	53	14.7	-1.1

Table 41 TEAE for SMQ analysis of pulmonary hypertension

	Ixazomib + LenDex (N=360)		Placebo + LenDex (N=360)	
	events	# of patients	events	# of patients
Dyspnea	35	32	39	35
Exertional dyspnea	14	12	24	20
Pulmonary hypertension	2	1	0	0
Pulmonary microemboli	1	1	0	0

8.5.7. Eye disorders

The incidence of TEAE within the system order class of eye disorders was 26.4% in ixazomib arm compared to 15.8% in the placebo arm. There were no grade 4 TEAE in this system order class. The TEAE, limited to the maximum severity for each patient, where the difference in incidence is greater than 2% are displayed Table 42. The final row, visual disturbance, is a grouping which includes the TEAE of vision blurred, visual impairment, visual acuity reduced, diplopia, blindness and myopia.

Table 42 TEAE in the system organ class of eye disorders

	Ixazomib + LenDex (N=360)				Placebo + LenDex (N=360)			
	All grades		Grade 3		All grades		Grade 3, 4, 5	
	n	%	n	%	n	%	n	%
Conjunctivitis	20	5.6	0	0	5	1.4	0	0
Dry eye	17	4.8	0	0	5	1.4	0	0
Vision blurred	20	5.6	0	0	12	3.3	0	0
<i>Visual disturbance</i>	28	7.8	0		20	5.6	0	0

8.5.8. PRES

Posterior reversible encephalopathy syndrome (PRES), formerly termed Reversible Posterior Leukoencephalopathy Syndrome has been reported with carfilzomib and bortezomib. A case of PRES is reported in the ixazomib development program in a drug-drug interaction study. The patient was a 65-year-old woman with a history of hypertension and myofibroblastic tumor with lung involvement. The patient had two cycles of treatment, cycle one included ixazomib and ketoconazole and cycle two included ixazomib only. An MRI was compatible with PRES, with the differential including hypertension, drug toxicity, vasculitis or infection. The patient discontinued ixazomib and the adverse event of PRES resolved approximately 3 weeks later.

8.5.9. Hypotension

Hypotension is a Warning and Precaution for bortezomib, another proteasome inhibitor. Based on analysis of preferred term and high level term hypotension is not a significant safety signal as displayed in Table 43. The high level term of vascular hypotension disorders includes the preferred term of cardiovascular insufficiency, hypotension and orthostatic hypotension.

Table 43 Hypotension

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Preferred Term							
Hypotension	23	17	4.72	20	15	4.17	0.56
High Level Term							
Vascular hypotensive disorders	26	20	5.56	26	20	5.56	0

8.5.10. Hepatic disorders

An SMQ analysis to evaluate for hepatic toxicity was done. The broader SMQs of hepatic disorders and drug related hepatic disorders – comprehensive search, did not demonstrate a significant safety signal. A potential safety signal is displayed with the SMQ of drug related hepatic disorders – severe events only. The analysis for these SMQs is displayed in Table 44. The preferred terms included in the drug related hepatic disorders – severe events only SMQ are drug-induced liver injury (2 patients), hepatic steatosis (2 patients), hepatitis cholestatic (1 patient), hepatocellular injury (2 patients), and hepatotoxicity (1 patient). While not a prominent safety signal, given the potential severity associated with a hepatic adverse event, the signal is worth noting.

Table 44 SMQ evaluation for Hepatic disorders

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Hepatic disorders	48	25	6.94	39	21	5.83	1.11
Drug related hepatic disorders – comprehensive search	48	25	6.94	38	20	5.56	1.39
Drug related hepatic disorders – severe events only	10	8	2.22	0	0	0	2.22

8.6. Specific Safety Studies/Clinical Trials

No studies or trials were conducted to evaluate a specific safety concern.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

An evaluation for the adverse event of malignancy was done. A broad SMQ of malignancies and pre malignant disorders did not reveal a safety signal as displayed in Table 45.

Table 45 Broad SMQ analysis for malignancy and premalignant disorders

	Ixazomib + LenDex (N=360)			Placebo + LenDex (N=360)			Risk difference
	events	# of patients	Proportion (%)	events	# of patients	Proportion (%)	
Malignancies	23	22	6.1	34	22	6.1	0
Premalignant disorders	4	4	1.1	5	4	1.1	0

Due to the association of malignancy and lenalidomide the applicant monitored for new malignancies during study treatment and follow up. The applicant notes new primary malignancies were reported in 9 patients in the ixazomib arm and 6 patients in the placebo arm during treatment and in follow up. In the ixazomib arm there were 1 myelodysplastic syndrome, 5 solid tumors including sigmoid colon, gallbladder, gastric, and undifferentiated and 3 skin cancers. In the placebo regimen there are 4 skin cancers, one myelodysplastic syndrome and one non small cell lung cancer.

During the end of phase 2 meeting, held Monday November 14, 2011, it was discussed with the applicant, that secondary to the safety signal of second primary malignancies associated with lenalidomide, it was recommended to the applicant to prospectively monitor for second primary malignancies during the trial and for at least 5 years after the last dose.

8.7.2. Human Reproduction and Pregnancy

Pregnant woman have not been exposed to ixazomib.

8.7.3. Pediatrics and Assessment of Effects on Growth

A pediatric population has not been exposed to ixazomib.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

During the trial there was one patient who had an accidental overdose of ixazomib. The patient took all 3 capsules (12 mg total) at once. The patient was admitted to the hospital. The patient was treated with gastric lavage, oral charcoal, intravenous fluids, and a laxative. The capsules were not retrieved. The patient did not have any AEs related to the overdose.

8.7.5. Subgroup Analysis

Evaluation of TEAE in certain subgroups was done. This evaluation is limited to TEAE displayed in Table 29. TEAE based on prior lines of therapy is displayed in Table 46. TEAE of North America compared to ROW is displayed in Table 47. TEAE based on creatinine clearance at baseline is displayed in Table 48.

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

Table 46 TEAE based on prior lines of therapy

Prior lines of therapy	Ixazomib + LenDex				Placebo + LenDex			
	1 prior line		2 or 3		1 prior line		2 or 3	
Total number of patients	211		149		212		148	
	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Thrombocytopenia	41	19.4	32	31.5	17	8.0	19	12.8
Gastrointestinal Disorders								
Diarrhea	90	42.7	61	40.9	85	40.1	45	30.4
Constipation	72	34.1	50	33.6	58	27.4	32	21.6
Nausea	48	22.7	44	29.5	41	19.3	33	22.3
Vomiting	44	20.9	35	23.5	19	9.0	20	13.5
General disorders and administration site conditions								
Peripheral edema	50	23.7	41	27.5	40	18.9	26	17.6
Pyrexia	22	10.4	24	16.1	39	18.4	30	20.3
Musculoskeletal and connective tissue disorders								
Muscle spasms	37	17.5	26	17.4	56	26.4	35	23.6
Psychiatric Disorders								
Insomnia	44	20.9	26	17.4	56	26.4	34	23
Skin and subcutaneous tissue disorders								
Rash (macular + maculo-papular)	22	10.4	29	19.5	22	10.4	10	6.8

Table 47 TEAE in N. America vs ROW

North America vs ROW	Ixazomib + LenDex				Placebo + LenDex			
	N. America		ROW		N. America		ROW	
Total number of patients	47		313		49		311	
	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Thrombocytopenia	15	31.9	58	18.5	4	8.2	32	6.0
Gastrointestinal Disorders								
Diarrhea	27	57.4	124	39.6	29	59.2	101	12.7
Constipation	14	29.8	108	34.5	12	24.5	78	11.1
Nausea	20	42.6	72	23	18	36.7	56	7.4
Vomiting	9	19.1	70	22.4	2	4.1	37	7.2
General disorders and administration site conditions								
Peripheral edema	17	36.2	74	23.6	15	30.6	51	7.6
Pyrexia	3	6.4	43	13.7	6	12.2	63	4.4
Musculoskeletal and connective tissue disorders								
Muscle spasms	15	31.9	48	15.3	18	36.7	73	5.0
Psychiatric Disorders								

North America vs ROW Total number of patients	Ixazomib + LenDex				Placebo + LenDex			
	N. America		ROW		N. America		ROW	
	n	%	n	%	n	%	n	%
Insomnia	8	17	62	19.8	15	30.6	75	6.4
Skin and subcutaneous tissue disorders								
Rash (macular + maculo-papular)	7	14.9	44	14.0	5	10.2	27	8.7

Table 48 TEAE Based on creatinine clearance

Creatinine Clearance Total number of patients	Ixazomib + LenDex				Placebo + LenDex			
	<60		≥60		<60		≥60	
	n	%	n	%	n	%	n	%
Blood and lymphatic system disorders								
Thrombocytopenia	22	27.8	51	18.1	10	10	26	10
Gastrointestinal Disorders								
Diarrhea	34	43	117	41.6	32	32	98	37.8
Constipation	26	32.9	96	34.2	29	29	60	23.2
Nausea	21	26.6	71	25.3	22	22	52	20.1
Vomiting	18	22.8	61	21.7	15	15	24	9.3
General disorders and administration site conditions								
Peripheral edema	24	30.4	67	23.8	24	24	41	15.8
Pyrexia	11	13.9	35	12.5	17	17	51	19.7
Musculoskeletal and connective tissue disorders								
Muscle spasms	11	13.9	52	18.5	22	22	68	26.3
Psychiatric Disorders								
Insomnia	13	16.5	57	20.3	17	17	72	27.8
Skin and subcutaneous tissue disorders								
Rash (macular + maculo-papular)	17	21.5	34	12.1	2	2	30	11.6

Intergraded Safety Population

As discussed in section 8.1, the pivotal trial C16010 served as the primary basis for the safety review. A total of 990 patients in 15 trials comprised the Intergraded Safety Population. As this population was not compared to a placebo controlled population, it is difficult to determine if the adverse events are due to ixazomib, the underlying disease or another drug. The TEAE which occurred in >20% of the intergraded safety population limited to the maximum severity for each treatment emergent adverse event per patient are displayed in Table 49. In general, the TEAE are similar to the pivotal trial.

Table 49 TEAE with > 20% incidence of the Intergraded Safety Population (N=990)

	All grades		Grades 1, 2		Grade 3-5	
	n	%	n	%	n	%
Blood and lymphatic system disorders						
Thrombocytopenia	246	24.8	88	8.9	158	16
Anemia	222	22.4	144	14.5	78	7.9
Neutropenia	213	21.5	58	5.9	155	15.7
Gastrointestinal disorders						
Diarrhea	412	41.6	344	34.7	68	6.9
Nausea	366	37.0	344	34.7	22	2.2
Vomiting	287	29.0	261	26.4	26	2.6
Constipation	278	28.1	273	27.6	5	0.5
General disorders and administration site conditions						
Fatigue	359	36.3	296	29.9	63	6.4
Peripheral Edema	236	23.8	216	21.8	20	2.0

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Post-market Experience

Ixazomib is not marketed in any country. There is no post-market safety information.

8.8.2. Expectations on Safety in the Postmarket Setting

In addition to routine surveillance expected, the applicant should continue to monitor for second primary malignancies as discussed in the end of phase 2 meeting.

8.9. Additional Safety Issues From Other Disciplines

There are no additional safety issues that were not discussed elsewhere in the review.

8.10. Integrated Assessment of Safety

The safety population was 720 patients treated with either ixazomib or placebo combined with lenalidomide and dexamethasone. The median number of cycles for the 360 patients on the ixazomib, lenalidomide and dexamethasone arm was 13 (range 1-26).

For the safety population the principle safety findings through 30 days after the last dose of study drug are:

- The addition of ixazomib to lenalidomide and dexamethasone did not result in an

increase in deaths with 3.3% of patients dying within 30 days of last dose on the ixazomib + LenDex arm compared to 4.7% on the placebo + LenDex arm.

- The more common serious adverse events overall were pneumonia and pyrexia.
- Ixazomib was associated with an approximately 1.5% increase risk of discontinuation from the trial or discontinuation of ixazomib due to a treatment emergent adverse event. There was an 11% increase in delay, holding, reduction, or discontinuation of ixazomib compared to placebo as a result of an adverse event.
- TEAE associated with a greater than 5% increase in incidence on the ixazomib + LenDex arm are vomiting, thrombocytopenia, constipation, peripheral edema, diarrhea, maculo-papular rash and nausea.
- The laboratory tests were the incidence of grade 3 and 4 abnormalities was greater than 5% on the ixazomib + LenDex arm are thrombocytopenia, lymphopenia and leukopenia.
- No clear dose-response and exposure-response for QTc was observed.
- The proportion of patients experiencing peripheral neuropathy was increased by 7.8% in the ixazomib, lenalidomide and dexamethasone arm.
- TEAE in the system order class of eye disorders was increased to 26.4% in the ixazomib + lenalidomide and dexamethasone arm compared to 15.8% in the placebo + lenalidomide and dexamethasone arm. The majority of these were conjunctivitis, dry eyes and vision blurred. There was an approximately 2.2% increase risk of visual disturbance with ixazomib.
- A potential safety signal is present for drug related severe hepatic disorders, which may be a class effect for proteasome inhibitors.

9 Advisory Committee Meeting and Other External Consultations

Ixazomib was not presented to the Oncologic Drug Advisory Committee or other external consultants because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment or prevention of a disease.

10 Labeling Recommendations

10.1. Prescribing Information

The following are recommended major changes to the ixazomib prescribing information based on this review:

1. Indications and Usage

- Added the fact that ixazomib is indicated in combination with lenalidomide and dexamethasone in the treatment of multiple myeloma in patients with at least

Clinical Review
Alexandria Schwarsin, MD
NDA 208462
Ninlaro (ixazomib)

one prior line of therapy.

2. Dosage and Administration

- Recommended the addition of dose modification guidelines for neutropenia and other non-hematologic toxicities.

1. Warnings and Precautions

- Recommended additional warnings and precautions of peripheral neuropathy, peripheral edema, cutaneous reactions, and hepatotoxicity.

6. Adverse Reactions

- A subsection to address ocular toxicities was recommended.

14. Clinical Studies

- Recommended the applicant add the updated progression free survival results to the prescribing information.

10.2. Patient Labeling

Review of Patient Labeling by the Division of Medical Policy Programs is ongoing at the time of this review.

11 Risk Evaluation and Mitigation Strategies (REMS)

The recommendation, based on the risk benefit profile of ixazomib, is no additional risk evaluation and mitigation strategies beyond routine post-marketing surveillance.

12 Post-marketing Requirements and Commitments

There are no post-marketing requirements or post-marketing commitments.

13 Appendices

13.1. References

1. Kumar, S.K., et al., Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*, 2014. 28(5): p. 1122-8.
2. Kumar, S.K., et al., Improved survival in multiple myeloma and the impact of novel therapies. *Blood*, 2008. 111(5): p. 2516-20.

13.2. Financial Disclosure

Clinical Review
 Alexandria Schwarsin, MD
 NDA 208462
 Ninlaro (ixazomib)

Covered Clinical Study (Name and/or Number): C16010

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>1,377</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>12</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>12</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in Sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEXANDRIA N SCHWARSIN
11/12/2015

ROMEO A DE CLARO
11/12/2015