15 September 2016
EMA/CHMP/594718/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NINLARO

International non-proprietary name: ixazomib

Procedure No. EMEA/H/C/003844/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Term
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reactions
AE	adverse event
ALT	alanine aminotransferase
API	Active pharmaceutical ingredient
AS	active substance
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC0-last	area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration
AUC0-216	area under the plasma concentration versus time curve from time zero to 216 hours postdose
AUC0-264	area under the plasma concentration versus time curve from time zero to 264 hours postdose
BCRP	breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BPI-SF	Brief Pain Inventory – Short-form
BSA	body surface area
CHMP	Committee for medicinal products for human use
CI	confidence interval
Cmax	maximum observed plasma concentration
CR	complete response
CrCL	creatinine clearance
CQA	Critical quality attribute
CSR	clinical study report
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
DOS	Design of experiments
ECOG	Eastern Cooperative Oncology Group
Emax	maximum inhibition
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
FLC	free light chain
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
GMP	Good manufacturing practice
HDT	high dose therapy
HLT	High-Level Term
HPLC	High performance liquid chromatography
HR	hazard ratio
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
ICP-MS	Inductively coupled plasma mass spectrometry
IDMC	independent data monitoring committee
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IR	Infrared
IRC	independent review committee
IRT	interdisciplinary review team
ISS	Integrated Summary of Safety
KF	Karl Fisher titration

Abbreviation	Term
LenDex	lenalidomide plus dexamethasone
LiHMDS	Lithium hexamethyldisilazane
LOD	Loss on drying
LS	least squares
MCC	Microcrystalline cellulose
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MMVAR/IFM	Multiple Myeloma Velcade at Relapse/Intergroupe Francophone du Myélome
MR	minimal response
MRP2	multidrug resistance protein 2
MS	Mass spectrometry
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	newly diagnosed multiple myeloma
NEC	not elsewhere classified
NMR	Nuclear magnetic resonance
NP-HPLC	Normal-phase HPLC
NSCLC	non-small cell lung carcinoma
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
ORR	overall response rate
PAR	Proven acceptable range
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PI	proteasome inhibitor
PK	pharmacokinetic(s)
PO	oral administration
PR	partial response
PT	preferred term
PVC	Poly(vinyl chloride)
QW	once weekly
RBC	red blood cell
RP2D	recommended phase 2 dose
RRMM	relapsed and/or refractory multiple myeloma
RVD	bortezomib in combination with lenalidomide and dexamethasone
SAE	serious adverse event
sCR	stringent complete response
SD	stable disease
SM	Starting material
SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
TFA	Trifluoroacetic acid
Tmax	time of first observed maximum plasma concentration
TTC	Threshold of toxicological concern
TTP	time to progression
TW	twice weekly
ULN	upper limit of normal
UPS	ubiquitin-proteasome system
UV	Ultraviolet
VGPR	very good partial response
VTD	bortezomib in combination with thalidomide and dexamethasone
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Takeda Pharma A/S submitted on 30 July 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for NINLARO, through the centralised procedure falling within Article 3(1) and point 4 of the Annex to Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2013.

NINLARO was designated as an orphan medicinal product EU/3/11/899 on 27 September 2011. NINLARO was designated as an orphan medicinal product in the following indication: treatment of multiple myeloma.

The applicant applied for the following indication: treatment for patients with multiple myeloma who have received at least one prior therapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ninlaro as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application. The applicant indicated that ixazomib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicant's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance ixazomib citrate contained in the above medicinal product to be considered as a new active substance, as they claimed that it was not a constituent of a product previously authorised within the Union.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14(9) of Regulation (EC) No 726/2004.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 15 December 2011. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: US.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 30 July 2015.
- Accelerated Assessment procedure was agreed upon by CHMP on 23 July 2015.
- The procedure started on 20 August 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 November 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 November 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- The PRAC assessment overview was adopted by PRAC on 3 December 2015.
- During the meeting on 17 December 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 December 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 11 February 2016.
- During the CHMP meeting on 25 February 2016, the CHMP concluded that it was no longer appropriate to pursue accelerated assessment as clinical major objections still remained and agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 1 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 16 March 2016.
- During the CHMP meeting on 30 March 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 1 April 2016, following an oral explanation on 30 March 2016, the CHMP agreed on a second List of Outstanding Issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 25 April 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 11 May 2016.
- During the meeting on 26 May 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to NINLARO.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Tuomo Lapveteläinen

- The applicant submitted written notice to the EMA on 2 June 2016 to request a re-examination of NINLARO CHMP opinion of 26 May 2016.
- During its meeting on 23 June 2016, the CHMP appointed Sinan B. Sarac as Rapporteur and Tuomo Lapveteläinen as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 20 July 2016 (Appendix 2 of Final Opinion). The re-examination procedure started on 21 August 2016.
- The Rapporteur's re-examination assessment report was circulated to all CHMP members on 23 August 2016. The Co-rapporteur's assessment report was circulated to all CHMP members on 19 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 31 August 2016.
- During a meeting of the SAG on 5 September 2016, experts were convened to consider the grounds for re-examination.
- During the CHMP meeting on 13 September 2016, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 15 September 2016, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of a conditional marketing authorisation.

2. Scientific discussion

2.1. Introduction

Multiple myeloma (MM) is a clonal disease of plasma cells that results in bone marrow failure, bone destruction, hypercalcaemia, anaemia, infection, renal failure, and neurological symptoms. It constitutes approximately 1% of all reported neoplasms and 13% of hematologic cancers worldwide (Palumbo A, 2011). In Europe, the estimated annual incidence is 38,930 new cases with approximately 24,290 deaths and the incidence is expected to increase over the next decade (Ferlay J, 2013).

Prognosis varies considerably on the basis of several factors, including the presence of cytogenetic abnormalities (Rajkumar 2011). MM with high-risk cytogenetic abnormalities, del(17), t(14;16) and/or

t(4;14), is characterized by short survival related to an early relapse rate and rapid development of mechanisms of resistance to multiple agents. Del(17), typically considered the ultra-high-risk group occurs in approximately 10-12% of patients with Refractory/Relapsed Multiple Myeloma (RRMM) (Avet-Loiseau 2010; 2012).

Treatment with cytotoxic drugs, such as alkylating agents and anthracyclines, and corticosteroids, was given in the past until the introduction of the first-in-class proteasome inhibitor (PI), bortezomib, and the immunomodulatory drugs (IMiDs), thalidomide and lenalidomide that led to improved outcomes. First line treatment options contain at least one of the novel therapies, i.e. proteasome inhibitors and/or immunostimulatory drugs, followed by autologous stem cell transplantation (ASCT), if indicated. Depth of response after autologous transplantation appears to correlate with the duration of disease control before disease progression occurs with the need for salvage therapy. In EU, bortezomib, thalidomide (as first line treatment) and lenalidomide are authorised in combination regimens for the treatment of multiple myeloma.

In the relapsed and/or refractory patients, bortezomib- and lenalidomide-based regimens are the most commonly used in combination with corticosteroids, to which sometimes also an alkylator or an anthracycline is added. In this setting, for patients who have received at least 2 prior therapies, including bortezomib and an IMiD, and have shown relapsed or refractory disease, pomalidomide (in combination with dexamethasone) and panobinostat (in combination with bortezomib and dexamethasone) are approved agents in the EU. The proteasome inhibitor carfilzomib and the monoclonal antibody elotuzumab both in combination with lenalidomide and dexamethasone were approved in the EU for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Ixazomib citrate, a prodrug, is the drug substance that rapidly hydrolyses under physiological conditions to its biologically active form, ixazomib. Ixazomib is an oral, highly selective and reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

Ixazomib induced apoptosis of several tumour cell types *in vitro*. Ixazomib demonstrated *in vitro* cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in multiple myeloma cell lines. *In vivo*, ixazomib demonstrated antitumour activity in various tumour xenograft models, including models of multiple myeloma. *In vitro*, ixazomib affected cell types found in the bone marrow microenvironment including vascular endothelial cells, osteoclasts and osteoblasts.

The sponsor applied for the following indication: Ninlaro is indicated for the treatment of patients with multiple myeloma who have received at least one prior therapy.

During the evaluation, the applicant revised the proposed indication as follows: NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have:

- experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+]; or

- experienced at least 2 relapses.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules. The capsules contain 2.3 mg, 3 mg and 4 mg ixazomib (as 3.3 mg, 4.3 mg and 5.7 mg ixazomib citrate, respectively).

As described in section 6.1 of the SmPC, other ingredients are:

Capsule contents: microcrystalline cellulose, magnesium stearate and talc;

Capsule shell: gelatin, titanium dioxide (E171), iron oxide (black, red and/or yellow iron oxide depending on capsule colour) (E172);

Printing ink: shellac, propylene glycol, potassium hydroxide, black iron oxide (E172).

Capsules are individually packaged in a PVC-Aluminium/ Aluminium blister sealed inside a wallet pack as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of ixazomib citrate is 2-[(1R)-1-[[2-[(2,5- dichlorobenzoyl) amino]acetyl]amino]-3-methylbutyl]-5-oxo-1,3,2-dioxaborolane-4,4-diacetic acid corresponding to the molecular formula $C_{20}H_{23}BCl_2N_2O_9$ and has a relative molecular mass of 517.12 g/mol. Ixazomib citrate has the following structure (**Figure 1**):

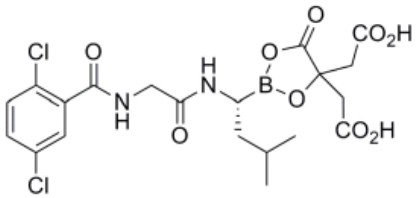


Figure 1 . Molecular structure of ixazomib citrate.

The active substance, ixazomib citrate, is a pro-drug of ixazomib. Under physiological conditions ixazomib citrate rapidly hydrolyses to ixazomib, which is a boronic acid of the general structure R-$B(OH)_2$.

Ixazomib citrate is a white to off-white non-hygroscopic powder, with a melting point ~ 231°C (with decomposition). Based on its high solubility and low permeability, ixazomib is a BCS Class 3 compound. Studies showed that ixazomib is highly soluble across a broad aqueous pH range that includes thephysiological pH range (1.2 to 6.85). The pKa and logP of ixazomib citrate could not be determined due to the hydrolysis of ixazomib citrate to ixazomib in aqueous systems.

The structure of ixazomib citrate has been confirmed by IR spectroscopy, high resolution mass spectrometry, elemental analysis, UV-Vis spectroscopy and single crystal X-ray crystallography. ^{1}H- and ^{13}C-NMR and mass spectroscopy demonstrated that ixazomib citrate exists as the cyclic citrate ester structure in anhydrous, aprotic solvents, and that the ester rapidly hydrolyzes to ixazomib (boronic acid) in dilute aqueous solutions in the absence of excess citric acid. Supplementary NMR

experiments confirmed the rapid kinetics of ixazomib citrate hydrolysis and the favored ixazomib equilibrium once exposed to aqueous conditions.

The structure of ixazomib citrate contains one chiral centre. The absolute stereochemistry of ixazomib citrate at the single chiral centre has been unambiguously determined as *R*. Enantiomeric purity of the active substance is controlled by NP-HPLC and acceptance limit of this specification has been set at < 0.5%.

A number of polymorphic crystal forms of ixazomib citrate were identified and characterized. One has been identified as the most thermodynamically stable form and was selected for development and commercial manufacture. This form has been demonstrated to be consistently manufactured by the proposed manufacturer using a controlled crystallization procedure. Polymorphism is controlled in the active substance specification by XRPD.

Manufacture, characterisation and process controls

The proposed synthesis of ixazomib citrate comprises a sequence commencing with the separate synthesis of two key intermediates. These intermediates are then combined and elaborated to yield ixazomib citrate.

The proposed starting materials are accepted as suitable starting materials for regulatory purposes. The proposed starting materials are well characterised and relatively simple molecules, which require a number of discrete synthetic steps interspersed with isolated intermediates, to prepare the active substance. As a result, there is sufficient opportunity for purging impurities or synthetic by-products. Comprehensive manufacturing development studies have been performed; an understanding of the nature and fate of impurities has been demonstrated. SM1 is a potential source of genotoxic impurities which has been adequately addressed by the applicant.

Three critical steps were identified as part of the quality risk assessment and appropriate controls were developed to maintain the consistency of the process and the quality of the active substance. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Key process intermediates that fail to achieve the desired product quality or due to process deviation may be reprocessed according to a described reprocessing procedure. The proposed reprocessing procedure was considered acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. A comprehensive description of the nature and origin of impurities has been provided, including those impurities identified as potential genotoxins. The purity profile is well described, including enantiomeric purity and residual solvents. A section has been devoted to the discussion on genotoxic impurities, since there are numerous structural alerts. Their limits are based on TTC approach according to ICH M7.

The manufacturing process was developed using a combination of conventional univariate studies and elements of QbD, such as risk assessment and multivariate design of experiments (DoE). Based on these studies, criticality of process parameters of the synthesis was assessed. Proven acceptable ranges (PARs) have been defined for these critical process parameters. Upon request, further details about DoE, risk assessment and data used for defining the PARs were provided and considered acceptable.

The manufacturing process for the active substance evolved during development. A number of syntheses were developed sequentially; all of which shared the same bond-forming sequence and had

similar impurity profiles. Differences between processes are minor. As a result, active substance produced by earlier processes are accepted as similar to the process proposed for commercialisation.

The primary container for the active substance was adequately described. Upon request, a specification for the primary bag used for bulk packaging was updated to include a specific identification test. Satisfactory declarations of compliance with EU Regulation 10/2011 and its amendments as well as the general requirements for food contact material, have been provided confirming its suitability.

Specification

The active substance specification includes tests for: appearance (visual), identity (FTIR, NP-HPLC), assay (RP-HPLC), impurities (RP-HPLC), enantiomeric Impurity (chiral HPLC), residual solvents (GC), water content (KF), ixazomib content (HPLC), elemental impurities (ICP-MS), particle size (laser diffraction) and polymorphic form (XRPD).

For the control of particle size, following the request from the CHMP, the applicant introduced a multi-point control. Since ixazomib citrate is sensitive to hydrolysis, water content is carefully controlled as part of the active substance specification.

Upon request of the CHMP, the applicant committed to develop and validate a new test method for controlling residual solvents and introduce a specification limit, in line with ICH Q3C(R5), in the active substance specification by the end of 2016. This specification will be applied to all GMP lots of ixazomib citrate used to manufacture commercial finished product for EU supply.

The specification proposed for the active substance manufacturer is acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the source and quality of the reference standards used for active substance and impurities has been presented.

Batch analysis data from development (n= 2), clinical (n=12) and process performance qualification lots (n=3) of the active substance are provided. All batches were manufactured at the intended commercial manufacturing site. Comparative batch analysis data from active substance manufactured by earlier processes in addition to that proposed for commercialisation was presented. As indicated above, data lots manufactured by earlier processes are considered representative of the proposed commercial process. Batch analytical data for all lots are consistent from batch to batch and comply with the proposed specification.

Stability

Stability data on six commercial scale batches of active substance manufactured by the proposed synthetic route stored for up to 24 months under long term conditions at 5°C and for up to 6 months under accelerated conditions at 25°C/60%RH, according to the ICH guidelines, were provided. This was supplemented by up to 36 months stability data at 5°C on two clinical batches produced using earlier processes.

The following parameters were tested*:* appearance, assay, impurities, enantiomeric impurity, ixazomib content, particle size distribution, polymorphic form and microbial enumeration tests. The analytical methods used were the same as for release and were stability indicating.

Under all storage conditions, minor variability but no significant changes were observed for any of the parameters tested.

Forced degradation studies have been performed on one batch. Samples were exposed to stress conditions including heat at 40°C and 50°C and humidity (open-dish) at 25°C/60%RH and 25°C/75%RH.Test parameters comprised assay, total impurities, water content, ixazomib content and particle size distribution. No significant changes were observed in any test parameter under these conditions.

A photostability study were performed in line with ICH guideline Q1B was also performed. Other than an apparent minor increase in an unspecified impurity from "not detected" to 0.06%, no change to any other test parameter was observed. Therefore, it is confirmed that ixazomib citrate is not sensitive to light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability data presented justify the proposed retest period of 48 months, when packaged in the proposed container and stored at 5°C.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Ninlaro is an immediate-release hard capsule formulation available in three strengths containing 2.3 mg, 3 mg or 4 mg of ixazomib (as ixazomib citrate). The different strengths are differentiated by the colour of the capsule (flesh/light pink for the 2.3 mg capsules; light grey for the 3 mg and light orange for the 4 mg capsules) and the printing.

As described in section 6.1 of the SmPC, other ingredients are:

Capsule contents: microcrystalline cellulose, magnesium stearate and talc;

Capsule shell: gelatin, titanium dioxide (E171), iron oxide (black, red and/or yellow iron oxide depending on capsule colour) (E172);

Printing ink: shellac, propylene glycol, potassium hydroxide, black iron oxide (E172).

The quality target product profile (QTPP) was defined as an immediate release oral dosage form containing 2.3 mg, 3.0 mg or 4.0 mg of ixazomib, with a shelf life of 3 years, to be administered once a day on days 1, 8 and 15 of a 28-day cycle and that meets compendial and other relevant quality standards.

The critical quality attributes identified were: appearance, identification, assay, uniformity of dosage units, purity, dissolution, water content, polymorphic form and particle size. Ixazomib citrate is a stable citrate ester, which, under physiological conditions, undergoes rapid hydrolysis to the biologically active boronic acid, ixazomib. The physicochemical attributes of the active substance, considered to impact the quality and manufacturability of the finished product, were taken in consideration during development.

Excipient choice is typical of solid oral dosage forms; all are controlled to the relevant Ph. Eur. monographs with supplementary in-house specifications where relevant.

Satisfactory excipient compatibility studies have been described as part of formulation development. Studies were conducted to confirm the excipient selection that could improve the manufacturability. Prototypes were made in gelatin shells with ixazomib citrate and the excipients to establish the final components and were placed on stability for 6 weeks at 40 °C/75% RH. The excipients chosen based on the best stability and manufacturability were microcrystaline cellulose, talc, and magnesium stearate.

The history of ixazomib capsules manufacturing process development including detailed information on the formulation was presented by the applicant. Blending optimisation studies were performed to define a robust blending process.

Three dosage forms have been used for phase 1 studies: ixazomib injection for iv use, ixazomib for injection, and an oral capsule. The solid oral capsule dose strengths 0.2, 0.5, and 2.0 mg were introduced to allow the patients to take multiple capsules in the multiple-rising dose studies.

During phase 1 clinical trials, studies were initiated to improve the stability and the manufacturability of the ixazomib capsule formulation.

Two capsules shell types were studied for use in the drug product. Drug product made with both types of capsules shells was stored in closed-bottle conditions. Both types of capsules showed similar ixazomib content over time; however, the gelatin capsules were more stable in accelerated conditions, with respect to related substances. Therefore, the gelatin capsule shells were selected.

Since one of the goals on the QTPP was to develop a single dose unit for patients, before the final dose strengths were determined for the pivotal clinical studies, the range of drug loads possible in the intended capsule size for this product was determined, and the blending operations for this range were optimized.

Several capsule color and ink options were also evaluated. They showed no effect on the ixazomib capsule stability, and based on these results the colour and ink to be used in the commercial presentations was chosen.

Two dissolution methods have been developed. The first was validated and used throughout product development and registration stability studies to gather information about drug product release and stability. A more discriminatory dissolution method was developed and validated for routine quality control use. The method is accepted, as comparative dissolution profiles for all phase 3 pivotal clinical lots, and an assessment of discrimination, have been provided by both methodologies.

The primary packaging is PVC-Aluminium/Aluminium blister. A description of the container closure components along with their specifications has been provided. For the primary packaging, the applicant has presented declarations of conformance with EU Directive 10/2011, as amended for food contact and the relevant requirements of the Ph. Eur. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process comprises blendingof the active substance with the excipients, followed by encapsulation and packaging. For all finished product presentations, the % content of active substance ranges exceeds 2%, thus this process may be considered to be standard.

Manufacturing process parameters requiring control have been identified and are considerd sufficient to control the quality of the finished product.

Product specification

The control specifications for the finished product at release and end of shelf-life include appropriate tests and limits for this kind of dosage form including: appearance (visual), identification (UV, HPLC), assay (HPLC), related substances (HPLC), water content (KF), content uniformity (HPLC), dissolution (Ph. Eur.) and microbial control (Ph. Eur.).

Control limits at end of shelf-life are equivalent to those at batch release with the exception of specified, unspecified and total related substances.

Upon request, the applicant tightened both the release and shelf-life specification for total impurities. Satisfactory controls for microbial enumeration have been proposed in line with Ph. Eur. recommendations for non-sterile products.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

The non-compendial analytical procedures for Ixazomib capsules have been validated in line with CPMP/ICH/381/95 (Validation of analytical procedures: Text and Methodology Q2 (R1)). Satisfactory information regarding the source and quality of the reference standards used in release and stability testing of ixazomib capsules has been presented.

Batch analysis data for a total of twenty-seven lots (nine lots of each dosage strength), which confirm compliance to the proposed control specification have been presented. All test results showed consistency within and between batches.

Stability of the product

Up to twenty-four months long term (5°C, 25°C/60%RH and 30°C/75%RH) and six months accelerated (40°C/75%RH) stability data for a total of nine commercial scale batches (three lots of each dosage strength), have been presented. The batches of Ninlaro are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

This was supplemented by up to 36 months stability data for clinical batches of 2.3, 3.0 and 4.0 mg ixazomib capsules stored at 5°C, 25°C/60%RH and 30°C/75%RH), and 6 months data under accelerated (40°C/75%RH) conditions. Clinical lots differ from registration lots only in minor aspects relating to screening steps during manufacture and the absence of an ink imprint on the capsule. All stability lots were manufactured at the proposed site for commercial manufacture (Haupt Pharma Amareg GmbH).

Storage conditions and stability time points conform to those of ICH guidance. Stability-indicating test parameters included appearance, identity, assay, related substances (including enantiomeric impurity), water content, dissolution, disintegration and microbial enumeration tests. The same analytical methods as proposed for commercial use were proposed, except for dissolution where the earlier method was used to generate the majority of data. Since comparable batch analysis data was provided, and neither of the dissolution media contains surfactant and conditions are not aggressive, the change in dissolution methodology during stability studies to that proposed for routine QC control of dissolution was deemed acceptable.

No significant change was observed in any of the parameters tested. Although for all strengths specified degradation products increased slightly over time under long term and accelerated storage conditions, the levels remained well below the proposed commercial specification. Therefore, the registration stability studies demonstrated that the 2.3, 3.0 and 4.0 mg ixazomib capsules remain within specification limits for all attributes for the duration of the proposed 36 month shelf-life at the proposed storage condition of "not more than 30°C. Do not freeze".

A long-term stability study on one batch of each strength, has also been conducted to confirm stability of the bulk packaged capsules at the long-term storage condition of 5 °C. Capsules were packaged for 24 months in the bulk packaging configuration. Samples were tested using the registration test methods for appearance, assay, related substances and water content and additional methods for ixazomib content, enantiomeric impurity, and disintegration. Data demonstrate that the capsules remain unchanged when stored for 24 months under long-term (5 °C) storage conditions, which support a 24-month bulk hold time.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay, related substances, ixazomib content and dissolution. No significant changes were observed in appearance, assay, ixazomib content and dissolution. A difference in related substances was observed between the control and exposed samples in both the 2.3 and 3.0 mg presentation (0.05 vs 0.08% in the control sample and in the exposed sample, respectively). Given the low level of the degradant and the understanding that it did not change in the ixazomib citrate photostability study, the presence of this degradation product was attributed to analytical variability rather than an actual material sensitivity to light. Levels of specified degradation products and impurity remained unchanged. The results confirmed that the product is not photolabile.

Stress stability studies were conducted on one batch of each dosage strength. Samples were exposed to high temperatures (50 °C and 60 °C) or high humidity (25 °C/60% RH and 25 °C/75% RH). No significant changes from initial appearance, assay, ixazomib content or dissolution were observed for the samples stored for up to 6 weeks under the above mentioned conditions. Some increase in total impurities was observed over the course of the studies at high temperatures but remained well below the proposed acceptance criteria, indicating that the capsules can tolerate some exposure to high heat. An increase in water content and in turn an increase in impurities was observed under humidity, indicating that ixazomib capsules should be protected from moisture.

Freeze cycling and heat cycling studies were also conducted on one batch from each strength packaged in the PVC-Al/Al blister, to evaluate the effects of temperature excursions on packaged capsules. For the freeze cycling study, samples were held at 0 °C for 3 days followed by a 3 day hold at 25 °C/60% RH for each cycle. For the heat cycling study, samples were held at 50 °C for 3 days followed by a 3 day hold at 25 °C/60% RH for each cycle. A total of 3 freezing or heat cycles were performed, with analysis for appearance, assay, related substances, water content and ixazomib content conducted at the conclusion of each cycle. No significant changes were observed at any of the conditions tested. Although an increase in water content was observed over multiple heating cycles, it remained below the specification limit.

Based on available stability data, the proposed shelf-life of 36 months and storage condition of "not more than 30°C. Do not freeze", as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

The only animal-derived material used in ixazomib capsules is the gelatin of the capsule shells. The gelatin can be from bovine and porcine sources. Valid TSE CEP from the supplier of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Ixazomib citrate is a new chemical entity. The active substance contained in Ninlaro, ixazomib citrate, is an ester prodrug, which rapidly hydrolyses to ixazomib under physiological conditions.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and there in turn lead to the conclusion that the product should have satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the proposed SmPC. Physiochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

To develop and validate a new test method for controlling residual solvents and update the specification for the active substance in line with ICH Q3C(R5) limits by the end of 2016. These specifications will be applied to all GMP lots of ixazomib citrate used to manufacture commercial finished product for EU supply.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal non-clinical studies were conducted in compliance with Good Laboratory Practice (GLP) regulations. All of the pivotal *in vivo* non clinical studies were conducted using oral administration.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In Vitro Pharmacodynamics

Selectivity and potency against the active sites of the 20S proteasome (Report RPT-01200)
The IC50 for ixazomib against the 20S proteasome ß1 (caspase-like), ß2 (trypsin-like), and ß5 (chymotrypsin-like) proteolytic sites was investigated using specific fluorogenic substrates in biochemical microtiter plate-based assays (**Table 1**). The potency and selectivity of ixazomib for the proteasome active was also investigated compared to bortezomib (**Table 1**).

Table 1. Summary of Ixazomib and Bortezomib Enzymology Results

Biochemical Assays	Ixazomib	Bortezomib
K_i (nM)		
β5	0.93 (0.64 – 1.4, n = 3)	0.55 (0.34 – 0.89, n = 3)
β5i	0.4	0.2
IC_{50} (nM)		
β5	3.4 (2.8 – 4.1, n = 3)	2.4 (2.0 – 2.9, n = 45)
β2	3500	1200
β1	31	24 (14.5 – 40, n = 12)

IC50 = concentration producing 50% inhibition; Ki = inhibition dissociation constant.
Note: Results are reported as geometric mean (95% confidence interval [CI], number of experiments). Data without CI are single determinations.

These results were corroborated in a subsequent study, where the inhibitory effects of ixazomib and bortezomib against the ß5 and ß2 sites of the proteasome were determined in the human HCT-116 colorectal tumour cell line (Report MLN9708-28351). Ixazomib and bortezomib showed > 98% inhibition of the ß5 activity of the proteasome in this assay (mean IC50 = 0.0075 and 0.0036 µM, respectively). Ixazomib and bortezomib inhibited the ß2 activity less potently (mean IC50 = 9.1 and 0.41 µM, respectively), with ixazomib minimally inhibiting ß2 function.

The selectivity of ixazomib was also tested against a panel of 7 serine proteases and 2 cysteine proteases, as peptidyl boronic acids are known to inhibit other proteases, especially serine proteases, in a sequence-dependent manner (**Table 2**).

Table 2. Ixazomib Protease Selectivity

Protease	IC_{50} (µM)
Chymotrypsin	> 100 (n = 2)
Trypsin	> 100
Elastase	19 (7.8 – 47, n = 3)
Thrombin	> 100
Plasmin	> 100
tPA	> 100
CFbetaXIIa	> 100
Cathepsin B	> 100 (n = 2)
Cathepsin L	> 100

CFbetaXIIa = F12 coagulation factor XII (Hageman factor); IC50 = concentration producing 50% inhibition; tPA =tissue plasminogen activator.
Note: Results are reported as geometric mean (95% confidence interval [CI], number of experiments). Data without CI are single determinations.

In additional selectivity screens, ixazomib had no effect on a panel of 103 kinases and 18 receptors (neurotransmitter, ion channel, and receptors of the brain and gut), with an IC50 > 10 µM for each.

The chemical structure of ixazomib contains a chiral centre, with the drug substance determined to be the R-enantiomer. The S-enantiomer, was synthesized separately and evaluated for potency against the ß5 site of purified human 20S proteasome. The IC50 of the S-enantiomer in this assay was 0.8245 µM, with a 95% CI of 0.293, indicating that it is a weaker inhibitor of the proteasome ß5 site than ixazomib (IC50 = 3.4 nM) by a factor of more than 200 fold.

Kinetic analysis of inhibition of the 20S proteasome (Report RPT-01200)

Ixazomib and bortezomib showed time-dependent inhibition of the 20S proteasome because of the formation of a covalent bond between the boronic acid and the hydroxyl of the *N*-terminal threonine side chain. The binding is reversible, and equilibrium between bound and unbound complexes is reached over time (

Table 3).

Table 3. 20S ß5 Binding Kinetics

Parameter	Ixazomib	Bortezomib
k_{on} ($sec^{-1}M^{-1}$)	700,000 (450,000 – 940,000, n = 3)	195,000 (140,000 – 250,000, n = 3)
k_{off} (sec^{-1})	0.00066 (0.00019 – 0.0011, n = 3)	0.00011 (0.000067 – 0.00015, n = 3)
β5 $t_{1/2}$ (minute)	18 (6.8 – 30, n = 3)	110 (71 – 150, n = 3)

koff =dissociation constant; kon = association constant; t1/2 = dissociation half-life.
Note: Results are reported as the mean (95% confidence interval [CI], number of experiments).

Effects on Proteasome Activity and Degradation of Proteasome Substrates (Report RPT-01200)
The ability of ixazomib to inhibit the proteasome and prevent proteasome-mediated degradation of substrate proteins was further explored in 3 separate cell-based assays. These cell-based assays characterized effects of ixazomib by examining the kinetics of inhibition and recovery of ß5 site activity in live cells; by examining the effects of ixazomib on a direct proteasome substrate, the 4xUb-Luciferase reporter; and by examining the effects of ixazomib on the NF- κB signaling pathway, which is known to be regulated by proteasome activity.

Using a cell-based assay to measure the effects of compounds on the ß5 site activity of the 20S proteasome in situ, the IC50 for ixazomib and bortezomib after 1 hour of treatment in Calu-6 cells was 9.7 and 3.0 nM, respectively; these values were comparable, within a 2- to 3-fold range, to those determined for purified 20S proteasome in the biochemical assay.

Recovery of proteasome activity after brief exposure to and washout of ixazomib and bortezomib was performed in the same assay system (**Table 4**).

The 4xUb-Luc cell-based reporter assay directly monitors the degradation of polyubiquitinated luciferase by the proteasome. Bortezomib is slightly more active in this assay than ixazomib (**Table 4**).

TNFα induced activation of the NF-κB pathway requires functional proteasome activity to degrade IκBα, an inhibitor of NF-κB. Proteasome inhibition prevents the degradation of IκBα and results in a decrease in NF-κB -driven gene expression. The NF-κB-Luc assay utilizes a reporter construct that expresses luciferase in an NF-κB-dependent manner. Ixazomib almost completely inhibited (99.3%) TNFα-induced activation of the NF-κB-Luc assay in HEK-293 cells, with an IC50 of 55 nM, compared to IC50 of 33 nM for bortezomib (**Table 4**).

Table 4. Ixazomib Proteasome Inhibition in Cultured Cells

Cell-Based Assay	Ixazomib	Bortezomib
Calu-6 Proteasome-Glo™[a] IC_{50} (nM)[b]	9.7	3.0
Calu-6 Proteasome-Glo (% Activity)[b, c]		
t = 4 hours, no washout	7.1 (3.6 – 10.6, n = 5)[d]	3.5 (2.0 – 4.9, n = 5)[c]
t = 4 hours, washout	69 (66 – 71, n = 5)[c]	20 (18 – 23, n = 5)[c]
MDA-MB-231 4 × Ub-Luc EC_{50} (nM)	525 (330 – 840, n = 4)	310 (230 – 400, n = 29)
E_{max} (fold stimulation)	265 (160 – 370, n = 4)[c]	370 (330 – 410, n = 29)[c]
HEK-293 NF-κB–Luc IC_{50} (nM)	55 (33 – 91, n = 7)	33 (27 – 40, n = 23)
Maximum inhibition (%)	99.3 (99.0 – 99.6, n = 7)[c]	99.6 (99.3 – 100, n = 23)[c]

EC50 = concentration producing half-maximal response; Emax = maximum effect; IC50 = concentration producing 50% inhibition
Note: Results are presented as the geometric mean (95% confidence interval [CI], number of experiments), except where otherwise noted. Data without CI are single determinations.
a Promega Corporation (Madison, WI, USA).
b This assay evaluated ß5 activity.
c After exposure to 1-µM ixazomib for 30 minutes.
d Results are presented as the mean (95% CI, number of experiments).

The potency and selectivity of ixazomib for proteasome active sites were also evaluated independently *in vitro* in cultured MM.1S cells. In MM.1S cells, ixazomib showed the greatest potency for the ß5 site, with an IC50 between 5 and 10 nM, and the least for the ß2 site, with an IC50 > 10 µM. Western blot analysis of protein extracts from MM.1S cells treated with 12-nM ixazomib showed a time- and dose-dependent increase in ubiquitinated proteins.

Viability Effects on Cultured or Primary Human Myeloma Cells (Report MLN9708-27528)
The *in vitro* viability effects of ixazomib were evaluated in the MM.1S, ANBL-6, RPMI-8226, and NCI-H929 human myeloma cell lines. In all cell lines, ixazomib was a potent inhibitor of viability, with inhibition occurring in a dose-dependent manner (**Table 5**).

Table 5. Effects of 72-hour ixazomib treatment on viability of human myeloma cell lines *in vitro*

Cell Line	Disease	n	LD_{50} Geometric Mean (µM)	SE
ANBL-6	Multiple myeloma	3	0.0243	0.0072
MM.1S	Multiple myeloma	5	0.0258	0.0360
RPMI-8226	Plasmacytoma; myeloma	11	0.0059	0.0017
NCI-H929	Plasmacytoma; myeloma	5	0.0149	0.0007

LD50 = concentration causing lethality for 50% of cells; SE = standard error.
Note: Data from at least 3 and up to 11 independent determinations are displayed as the geometric mean, along with the associated SE.

Additionally, the *in vitro* anti-tumour activity of ixazomib was independently evaluated using MTT assays in a variety of cultured human MM cell lines: MM.1S, MM.1R, RPMI-8226, OPM1, OPM2, NCI-H929, and INA-6.

The cultured human MM cell lines were assessed for cell viability after treating cells with ixazomib (6.25, 12.5, 25, or 50 nM) for 48 hours. A significant concentration-dependent decrease ($p < 0.05$; n = 3) in cell viability resulted. In MM.1S, MM.1R, and NCI-H929 cells, treatment with 12.5-nM ixazomib resulted in approximately 50% loss of viability compared to control cells, while treatment with 25-nM

ixazomib resulted in > 90% loss of viability in these lines and in RPMI-8226 and INA-6. OPM1 and OPM2 lines were less sensitive to ixazomib, with only 40% to 50% loss of viability at 25-nM ixazomib.

A significant dose-dependent decrease ($p < 0.001$) in viability was also observed after ixazomib treatment (12, 25, or 50 nM) for 24 or 48 hours in primary myeloma cells purified by CD138+ selection from 6 MM patients, including patients relapsing after previous treatment with bortezomib, lenalidomide, and/or dexamethasone. A 24-hour treatment with 25-nM ixazomib resulted in approximately 40% loss of viable cells in the 6 patient samples tested, and 50-nM ixazomib resulted in at least 70% loss of viable cells in 4 of the 6 patient samples. The effects on viability were greater with the 48-hour treatment. These concentrations of ixazomib had a much weaker effect on PBMCs from healthy donors. Treatment with 25-nM ixazomib for 48 hours resulted in < 10% loss of viability in 5 of 6 PBMC samples evaluated and approximately 20% loss in 1 sample. At 50-nM ixazomib, the maximal viability loss was approximately 30% in 5 of 6 PBMC samples, with approximately 40% loss in the remaining sample.

Proliferation of MM cells is stimulated by co-culture with bone marrow stromal cells, which provide supportive cytokines. Ixazomib inhibited proliferation of MM.1S cells cultured in the presence of bone marrow stromal cells, which were derived from CD138- cells purified from bone marrow of MM patients. In the presence of bone marrow stromal cells (BMSCs), 25-nM ixazomib caused an approximately 15-fold decrease in tritiated thymidine uptake compared to control-treated cells, and 12.5-nM ixazomib also significantly reduced tritiated thymidine uptake, by approximately 2.5-fold.

Mechanistic Effects on Cellular Pathways in Multiple Myeloma Cell (Chauhan D, et al, 2011)

The effects of ixazomib on apoptotic signalling pathways were evaluated *in vitro* in human MM cells using Western blot analysis. After ixazomib treatment in NCI-H929 and MM.1S cells, there was an increase in proteolytic cleavage of caspase-3, caspase-8, caspase-9, and PARP, indicating that ixazomib triggered both intrinsic mitochondria-dependent (caspase-9) and extrinsic mitochondria-independent (caspase-8) signalling pathways. Although the complete series of events leading to apoptosis of MM cells treated with proteasome inhibitors is not fully characterized, several pathways are frequently activated in response to other proteasome inhibitors, including bortezomib; these pathways include ER stress/UPR, upregulation of pro-apoptotic BH3-only proteins, and p53 activation. Ixazomib treatment of MM.1S cells resulted in an increase in protein levels of p53- and p53-regulated genes, including p21, which is involved in cell cycle arrest, and the pro-apoptotic BH3-only proteins NOXA and PUMA. Proteasome inhibition triggered by ixazomib also increases levels of the chaperone protein BiP, increases the phosphorylation of eIF2alpha, and increases levels of the transcription factor CHOP, all of which are signs of the UPR.

Effects of Ixazomib on Additional Cell Types Present in the Bone Marrow Microenvironment (Garcia-Gomez et al, 2014)

Ixazomib was evaluated for its ability to inhibit the *in vitro* formation of capillary-like tube structures from HUVECs, a process which provides an *in vitro* model of angiogenesis. Ixazomib inhibited tube formation, as quantitated by the number of branch points per field of view, which decreased by approximately 35% in the presence of ixazomib.

In vitro studies of osteoclastogenesis showed that ixazomib inhibited the formation of osteoclasts from precursors in PBMCs of healthy donors and MM patients. These experiments identified concentrations of ixazomib (2.5 to 10 nM) which significantly inhibited osteoclast formation without reducing the total number of cells, indicating an effect on differentiation of osteoclasts rather than viability. However, a higher concentration of ixazomib (25 nM) did decrease total cell number along with osteoclast formation. The bone resorptive capacity of osteoclasts was evaluated *in vitro* in the presence and

absence of ixazomib and bortezomib. Ixazomib reduced calcium resorption at concentrations of ≥2.5 nM. Bortezomib showed similar effects on osteoclastogenesis in these assays at lower concentrations.

In vitro studies of osteoblast differentiation and function showed that ixazomib promotes osteoblastic differentiation from progenitor cells and stimulates matrix mineralization. Primary MSCs from bone marrow of patients with MM were differentiated in osteogenic media in the presence or absence of ixazomib or bortezomib. Cells were evaluated for characteristics of osteoblasts including alkaline phosphatase (ALP) activity, a surrogate marker of early-stage osteoblasts, and matrix mineralization, the ability to deposit calcium in the extracellular environment. After 11 days in osteogenic media, ALP increased in a dose-dependent manner in the presence of ixazomib or bortezomib, with significantly increased ALP observed at concentrations of ixazomib of ≥2.5 nM. After 21 days in osteogenic media, calcium deposition was increased in the presence of ixazomib or bortezomib.

Combination effect of ixazomib and lenalidomide on viability of multiple myeloma cell lines grown in vitro (Report MLN9708-30663)

The effect of ixazomib in combination with lenalidomide was tested in 4 MM cell lines, MM1.S, ANBL-6, RPMI-8226, and NCI-H929. Ixazomib was a potent inhibitor of viability in all cell lines (**Table 6**). Lenalidomide, showed differential potency among 4 cell lines. While lenalidomide induced cell death in ANBL-6, NCI-H929, and RPMI-8226, no effect on cell viability was observed in MM1.S at concentrations up to approximately 25 µM.

The combination of ixazomib and lenalidomide was synergistic in ANBL-6 and NCI-H929 cells and additive in MM.1S and RPMI-8226 cells. The synergistic and additive categories were determined by using 2 types of combination measures, combination index and nonlinear blending.

Table 6. Summary of Single Agent and Combination Measures with Interpretation

Cell Line	Compound	Findings	Interpretation
MM1.S	Ixazomib	EC_{50}: 23.9 nM	
	Lenalidomide	EC_{50}: > 24,900 nM	
	Ixazomib and Lenalidomide	Combination index: N/A Nonlinear blending: 0	Additive
ANBL-6	Ixazomib	EC_{50}: 17.7 nM	
	Lenalidomide	EC_{50}: 578 nM	
	Ixazomib and Lenalidomide	Combination index: 0.45, $p < 0.001$ Nonlinear blending: 21.3, $p < 0.001$	Synergistic
NCI-H929	Ixazomib	EC_{50}: 18.3 nM	
	Lenalidomide	EC_{50}: 776 nM	
	Ixazomib and Lenalidomide	Combination index: 0.48, $p < 0.001$ Nonlinear blending: 23.6, $p < 0.001$	Synergistic
RPMI-8226	Ixazomib	EC_{50}: 7.85 nM	
	Lenalidomide	EC_{50}: 447 nM	
	Ixazomib and Lenalidomide	Combination index: N/A Nonlinear blending: 18.9, $p < 0.001$	Additive

EC50 = concentration producing a half-maximal response; N/A = not applicable.
Note: For combination index: when $p < 0.05$, combination index is defined as follows: synergy (CI 0-0.7); additivity (CI 0.7-1.3); subadditivity (CI 1.3 - 2); antagonism (CI >2). If a conclusion cannot be made using combination index (CI), the nonlinear blending value (NLB) is used. When $p < 0.05$, NLB is defined as follows: synergy (NLB > 20); additivity (NLB between -20 and 20); antagonism (NLB < -20). When $p > 0.05$ for CI or NLB, the result is scored as inconclusive.

In Vivo Pharmacodynamics

Pharmacokinetics and pharmacodynamics in a multiple myeloma mouse model after oral or intravenous administration (Report MLN9708-24699)

The PK and pharmacodynamic properties of ixazomib were evaluated after PO or IV administration to female CB-17 SCID mice bearing MM.1S xenografts. Mice were administered a single IV or PO dose of vehicle (5% hydroxypropyl-beta-cyclodextrin [HP-ß-CD]), a single IV dose of ixazomib at 2.0 mg/kg, or a single PO dose of ixazomib at 6.0 mg/kg. Groups of 3 mice were euthanized at 4 hours after the vehicle dose, and at 0.25, 0.5, 1, 4, 8, or 24 hours after the ixazomib dose.

Intravenous administration of 2-mg/kg ixazomib and PO administration of 6-mg/kg ixazomib resulted in plasma AUC24 1100 and 1680 hr*ng/mL respectively and tumour AUC24 15,800 and 16,100 hr*ng/mL, respectively.

Administration of ixazomib by either route resulted in pharmacodynamic effects in MM.1S xenograft tumours. A pharmacodynamic effect, as measured by percent proteasome inhibition (I%) of the 20S proteasome ß5 site, was observed by 1 hour postdose, and inhibition persisted compared to baseline through 24 hours. The mean observed Emax for 20S proteasome inhibition in tumour tissue was 71.7 I% (at 4 hours) and 60.6 I% (at 8 hours) after IV and PO administration, respectively. The mean area under the effect-time curve from time 0 to 24 hours (AUE24) in tumour tissue was 1530 and 1210 hr*I% after IV and PO administration, respectively.

Additionally, markers of the UPR that occurs after proteasome inhibition (ATF-3 and GADD34, as detected by IHC and Western blot analysis, respectively) were elevated by 4 hours post-dose and remained above baseline through 24 hours. By 8 hours post-dose, IV and PO administration both resulted in elevated levels of cleaved caspase-3; a marker of apoptosis evaluated by Western blot analysis and remained elevated through 24 hours.

Anti-tumour activity in a multiple myeloma mouse model after oral administration (Report MLN9708-24176-001A)

Female CB-17 SCID mice bearing MM.1S xenografts were orally administered vehicle (5% HP-ß-CD) or ixazomib at 1, 2, 4, 6, 8, or 10 mg/kg BIW for 18 days (5 doses) (n = 5/ixazomib group and 8/vehicle group). Treatment began on Day 1, when mean tumour volumes (MTVs) reached approximately 100 to 350 mm^3. Tumour growth inhibition (TGI) was determined on Day 19 by calculating the percent TGI ([MTV of the control group - MTV of a treated group]*100 / [MTV of the control group]).

Ixazomib administered at 6, 8, and 10 mg/kg resulted in statistically significant anti-tumour activity compared to vehicle treatment (TGI = 99.3%, 99.7%, and 100%, respectively; change in the area under the tumour volume-time curve (ΔAUC), p = 0.001 for all doses). At 6 and 8 mg/kg, tumour volume at Day 19 was less than that on Day 0; at 10 mg/kg, there were no measurable tumours on Day 19. At 1 and 4 mg/kg, weaker (but still statistically significant) anti-tumour activity was observed (TGI = 26.3% and 30.8%, respectively; ΔAUC, p = 0.005 for both doses). However, ixazomib at 2 mg/kg did not show statistically significant anti-tumour activity (TGI = 9.1%; ΔAUC, p = 0.05). Mice at 8 mg/kg exhibited a maximum mean body weight loss of 11.2% on Day 11, and 1 mouse at 10-mg/kg was removed from study on Day 7 as a result of body weight loss exceeding 15%.

Anti-tumour activity in a multiple myeloma mouse model after intravenous administration (Report MLN9708-24177)

Female CB-17 SCID mice bearing MM.1S xenografts were IV administered vehicle (5% HP-ß-CD) QW (3 doses); ixazomib at 0.5, 1.0, 2.5, or 7.0 mg/kg BIW for 18 days (6 doses); or ixazomib at 0.82, 1.64, 4.1, or 11.47 mg/kg QW (3 doses). Dosing was initiated on Day 0 when MTVs reached approximately 100 to 350 mm^3. Tumour growth inhibition was determined on Day 19 by calculating

the percent TGI ([MTV of the control group - MTV of a treated group] *100 / [MTV of the control group]).

Ixazomib administered IV BIW at 0.5, 1.0, 2.5, and 7.0 mg/kg resulted in anti-tumour activity compared with vehicle treatment (TGI = 34.2%, 46.8%, 94.2%, and 99.3%, respectively; ΔAUC, p = 0.001 at all doses except 0.5 mg/kg [p < 0.05]). In both the 2.5- and 7.0-mg/kg groups, strong anti-tumour activity resulted in tumour volumes that were smaller at the end of the study than at the beginning of treatment, and some tumours were no longer visible or measurable in the 7.0-mg/kg group.

Ixazomib administered IV QW at 0.82, 1.64, 4.1, and 11.47 mg/kg also resulted in anti-tumour activity compared with vehicle treatment (TGI = 24.7%, 93.2%, 97.1%, and 99.5%, respectively; ΔAUC, p < 0.001). In the 1.64-, 4.1-, and 11.47-mg/kg groups, strong anti-tumour activity resulted in tumour volumes that were smaller at the end of the study than at the beginning of treatment, and some tumours were no longer visible or measurable in the 4.1- and 11.47-mg/kg groups.

The maximum mean body weight change of -11.3% was seen in the 11.47-mg/kg ixazomib IV QW group on Day16. No mice were removed from the study as a result of body weight loss.

Effects on survival, splenomegaly, and igg2a levels in the imyc^{ca}/bcl-xl genetically engineered mouse model of de novo plasma cell malignancy (Report RPT-01431)

Male and female iMyc^{Ca}/Bcl-XL mice were either left untreated or administered ixazomib at 18 mg/kg IV BIW or bortezomib at 1.2 mg/kg IV BIW for 6 consecutive weeks (treatment phase) (n = 30). These doses represent the MTD for each drug in non-transgenic (B6xFVB/N) F1 hybrid mice. After the treatment phase, mice were monitored for an additional 25 weeks. A hazard ratio > 1 indicated an advantage of treatment over untreated controls.

Untreated iMyc^{Ca}/Bcl-XL mice invariably developed de novo PCM with short onset (median overall survival = 112 days) that was accompanied by splenomegaly (mean spleen weight = 0.87 g). Ixazomib treatment at 18 mg/kg IV BIW prolonged survival (overall survival = 148 days; hazard ratio = 0.116; 95% CI = 0.057 to 0.236; p < 0.0001) and reduced splenomegaly (mean spleen weight = 0.63 g; p < 0.05) compared to untreated controls. Bortezomib treatment at 1.2 mg/kg IV BIW similarly prolonged median overall survival (139 days; hazard ratio = 0.163; 95% CI = 0.085 to 0.312; p < 0.0001) and alleviated splenomegaly (mean spleen weight = 0.59; p < 0.05).

Mean plasma IgM levels were also elevated in iMyc^{Ca}/Bcl-XL mice compared to hybrid (B6x FVB/N) F1, age-matched non-transgenic mice (IgM = 1.59 x 10^6 versus 3.8 x 10^4 ng/mL in iMyc^{Ca}/Bcl-XL and nontransgenic mice, respectively; p <0.05). IgM levels were as follows in this PCM model : IgM = 3.97x 10^5 and 3.03x10^5 ng/mL with ixazomib and bortezomib, respectively; p >0.05. Levels of IgA, IgG1, and IgG2b were not significantly elevated in this transgenic model and were not affected by treatment with ixazomib or bortezomib (p > 0.05).

In all study groups, the mean maximum body weight loss was < 10%.

Effects on tumour burden and osteolytic lesions in the DP54-Luc disseminated mouse model of iMyc^{Ca}/Bcl-XL plasma cell malignancy (Report RPT-01432)

DP54 is a mouse plasma cell tumour line derived from the bone marrow of a syngeneic F1 (B6xFVB/N) mouse previously inoculated with an iMyc^{Ca}/Bcl-XL tumour. *In vitro*, DP54 cells express the iMyc^{Ca} and Bcl-XL transgenes, and various late B-cell and early plasma cell markers including CD38, CD138, and B220, and have a gene expression profile very similar to human MM. The DP54 cells were stably transfected with firefly luciferase so they could be visualized by bioluminescent imaging of live animals.

DP54-Luc iMyc^{Ca}/Bcl-XL PCM cells were inoculated IV in the tail vein of female non-obese diabetic (NOD)-SCID mice, resulting in disseminated disease. Tumour burden was monitored weekly by measuring total photon flux using quantitative bioluminescence Xenogen imaging. When the total photon flux reached a baseline level on Day 6, mice were dosed with vehicle (5% HP-ß-CD) IV BIW, ixazomib at 11 mg/kg IV BIW, ixazomib at 3 mg/kg SC once daily (QD), or bortezomib at 0.7 mg/kg IV BIW (n=10 mice/group [on Day 20, n=9 in the SC ixazomib group; on Day 23, n=9 in the vehicle, bortezomib, and SC ixazomib groups and n=5 in the IV ixazomib group]). These doses represent the MTD in NOD-SCID mice. A total of 5 doses were administered in the IV dose groups and a total of 15 doses were administered in the SC dose group. Tumour burden was measured on Days 6, 13, 20, and 23. Anti-tumour activity was determined by calculating the treatment over control (T/C) ratio of the mean photon flux measurement (tumour burden) on Day 20. In addition, cranial suture widening, a sign of osteolytic bone disease, was assessed on Day 23 after euthanasia by measuring sagittal suture separation area (SSSA) using computed tomography (CT) imaging.

Anti-tumour activity was shown in all 3 treatment groups compared to the vehicle group: ixazomib at 11 mg/kg IV BIW (T/C=0.36, p<0.05), ixazomib at 3 mg/kg SC QD (T/C=0.24, p<0.05), and bortezomib at 0.7 mg/kg IV BIW (T/C=0.52, p<0.05).

Ixazomib treatment at 11 mg/kg IV BIW also reduced cranial suture widening by 27% (SSSA=0.85 ±0.16 mm2) compared to vehicle treatment (SSSA =1.16 ± 0.04 mm^2) (p< 0.05). In contrast, bortezomib at 0.7 mg/kg IV BIW had no significant effect on SSSA (1.17 ±0.08 mm^2) compared to vehicle treatment (p >0.05). SSSA for ixazomib SC QD was not determined in this study. No treatment group dosed with ixazomib or bortezomib exhibited a mean maximum body weight loss of >5%.

Anti-tumour activity in a DP54-Luc intratibial mouse model of a plasma cell malignancy derived from a genetically engineered mouse model (Report RPT-01433)

Female nude mice were inoculated with DP54-Luc iMyc^{Ca}/Bcl-XL PCM cells into the bone marrow space of the tibia. Mice were treated IV BIW with 5% HP-ß-CD, ixazomib at 13 mg/kg, or bortezomib at 0.8 mg/kg for 3 consecutive weeks. These doses represent the MTDs in female nude mice. Treatment began on Day 10. Anti-tumour activity was determined by calculating the T/C ratio of the mean photon flux measurement (tumour burden) on Day 29. Ixazomib treatment at 13 mg/kg IV BIW showed significant anti-tumour activity (T/C= 0.05, p< 0.05) compared to vehicle treatment. Bortezomib treatment at 0.8 mg/kg IV BIW showed similar anti-tumour activity (T/C= 0.02, p< 0.05). No treatment group exhibited a mean maximum body weight loss of >5%.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been conducted (see discussion on non-clinical aspects).

Safety pharmacology programme

In vitro, ixazomib (0.00508 to 100 µM) weakly inhibited the cloned cardiac potassium (K^+) hERG channel in HEK-293 cells with a Ki of 24.9 µM and an IC50 of 59.6 µM. The ixazomib concentration (Ki of 24.9 µM) associated with *in vitro* hERG activity is >190-fold the human Cmax of approximately 0.13 µM at the clinical phase 3 dose of 4 mg administered QW for 3 weeks on a 28-day cycle (the multiple is significantly greater when accounting for human plasma protein binding).

A telemetry *in vivo* study was performed in beagle dogs to evaluate the effects of ixazomib on the CVS. ECG, nervous system, and respiratory evaluations were also conducted as part of GLP-compliant repeated-dose toxicology studies in rats and dogs. No treatment-related effects on blood pressure, heart rate, or ECG parameters (including PR interval, QRS duration, QT interval, and corrected QT

[QTc] interval) were observed at any time point at any dose. In conclusion, ixazomib had no effects on the CVS in conscious dogs at single doses up to the highest dose administered, 0.21-mg/kg ixazomib.

Safety Pharmacology Assessments in Repeated-Dose Toxicology Studies

In GLP-compliant repeated-dose toxicology studies, ixazomib had no overt effects on the respiratory systems of rats or dogs. In dogs, PO doses ≥ 0.10 mg/kg (BIW for 2 weeks, followed by a 10-day non-dosing period; 21-day cycle) resulted in microscopic neuronal findings including degeneration of the sympathetic, dorsal root, peripheral autonomic, and end organ ganglia, and secondary axonal/nerve fibre degeneration of the peripheral nerves and ascending tracts in the dorsal columns of the spinal cord. Occasionally, microscopic findings correlated with clinical signs of ataxia, wide-based stance, and decreased reflexes. In the 9-month dog study (10 cycles) where the dosing regimen mimics the clinical regimen (28-day cycle), similar microscopic neuronal findings were observed at 0.20 mg/kg (AUC_{24} 1870 hr*ng/mL). There were no changes in neuronal function detected in the neurobehavioral functional assessment. The majority of neuronal findings were reversed or reversing after a recovery period, with the exception of findings in the dorsal root ganglia (DRG) and spinal cord.

There were no effects on ECG parameters in the 1-, 5-, or 10-cycle PO, and 2- or 5-cycle IV studies in dogs. Potential increases in QTc were observed in male dogs in the 1-cycle PO study at 0.1 mg/kg (Day 11 AUC_{24}=159 ng/mL); however, increased QTc was not observed in female dogs in this study nor in any dogs in the 2-cycle IV study that had Cmax exposures that were similar or greater than those of the male dogs with potential increases in the 1-cycle PO study.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

The PK of ixazomib was evaluated after PO and IV administration of ixazomib citrate or ixazomib to Sprague-Dawley rats, New Zealand white rabbits, beagle dogs, and cynomolgus monkeys. PK was also evaluated in tumour-bearing mouse models.

Sensitive and selective LC/MS/MS methods were developed and validated in rat, rabbit, and dog plasma. These methods were used to determine the plasma concentrations of ixazomib in rats, rabbits, and dogs for the GLP-compliant TK studies with a LLOQ of 2.00ng/mL. Concentrations of ixazomib in mouse, rat, and dog whole blood and plasma samples in non-GLP-compliant PK and TK studies were determined using a non-validated LC/MS/MS method, with an LLOQ of 2.00 ng/mL.

Absorption

Caco-2 permeability and efflux transporter interactions of ixazomib
In a non-GLP-compliant study in the Caco-2 cell model, ixazomib showed moderate permeability and appeared to be a low-affinity substrate for efflux pumps. The apparent permeability coefficient (Papp) of ixazomib in Caco-2 cells at pH 7.4 was 2.0 $x10^{-6}$ and 5.8x 10^{-6} cm/sec in the apical-to-basolateral (A-to-B) and basolateral-to-apical (B-to-A) directions, respectively, at 5 µM, and 2.2 x $^{10-6}$ and 6.8 x $^{10-6}$ cm/sec in the A-to-B and B-to-A directions, respectively, at 50 µM.

When ixazomib (5 µM) or ixazomib citrate (10 µM) was incubated with known efflux pump inhibitors, GF120918 (an inhibitor of P-gp and BCRP), LY335979 (an inhibitor of P-gp), Ko143 (an inhibitor of BCRP), and indomethacin (an inhibitor of MRP2), the efflux ratio of ixazomib was reduced more than 2 fold with GF120918 or LY335979, but less than 2 fold with Ko143 or indomethacin.

Absorption of ixazomib after a single oral dose

In fasted rats (n=6), oral bioavailability was 41% and 34% in plasma and blood, respectively, after a single PO dose of 0.8-mg/kg ixazomib in 10% HP-ß-CD. The fraction of ixazomib absorbed (Fa) was approximately 60%, as determined by comparing the dose-normalized blood AUC24 after PO administration and intraportal vein (IPV) infusion.

In fasted rabbits (n =3/group), oral bioavailability was 18.8% and 20.0% in plasma and blood, respectively, after a single PO dose of 0.2-mg/kg ixazomib citrate reconstituted in Water for Injection (WFI) and formulated in55-mM citrate buffer and 3% glycine, pH 5.8.

In 2 separate studies in fasted dogs, ixazomib had oral bioavailability of 72.2% in plasma [n =3/sex] and 105% in blood [n =3 males]) after a single PO dose in a citrate buffer solution, indicating complete absorption. With a clinical prototype capsule formulation of ixazomib citrate, the oral bioavailability of ixazomib was approximately 130% on the basis of the plasma AUC24 ratio (capsule-to-IV, using the IV data from Report RPT-01151). After a single PO administration of either ixazomib in citrate buffer or ixazomib citrate capsule, the PK profiles at the post-absorption phase were overall similar to those after a single IV administration of ixazomib in citrate buffer.

Absorption after PO administration was rapid in plasma in both rats and dogs, with a tmax in the range of 0.42 to 1.0 hours, and slow in rabbits (tmax =24 hours).

Distribution

The concentrations of ixazomib derived radioactivity in tissues and its affinity for various tissues were determined after single PO or IV administration of [14C]ixazomib or [14C]ixazomib citrate to rats. The highest concentrations of 14C among all tissues were observed at 0.5 hours post-dose in 21 tissues. In blood, the highest concentration of drug-derived radioactivity was 0.439 µg equiv/g, observed at 0.5 hours post-dose; in plasma, the highest concentration of total drug-derived radioactivity was 0.250 µg equiv/g, also observed at 0.5 hours. The tissues with the lowest relative concentrations (≤ 0.03 µg equiv/g) at tmax were the brain, spinal cord, testis, bone, and eye lens. For most tissues, elimination was nearly complete by 672 hours post-dose, with trace amounts of radioactivity still observed in most tissues; concentrations in the brain (all regions), DRG, white adipose, bone, esophagus, and eye lens were all below the quantitation limit (BQL). Drug-derived radioactivity was found in melanin-containing tissues (eg, pigmented skin and the uveal tract of the eye), but the concentrations decreased in a manner similar to that seen with other tissues during the study and a specific association of radioactivity to melanin was not obvious.

In a QWBA study in albino rats, [14C]ixazomib (mean dose of 0.30 mg/kg [free acid] [approximately 42.3 µCi/kg], formulated in a solution of 10% HP-ß-CD and water) was administered once IV to 6 male Sprague-Dawley rats. Drug-derived radioactivity was widely distributed to tissues and retained in most tissues to the last sampling time point. The highest concentrations of 14C among all tissues were observed at 10 minutes post-dose in 14 tissues or 1 hour post-dose in 12 tissues. Tissues with 14C concentrations > 1.0 µg equiv/g at tmax were the cecum and cecum contents (1.070 and 3.585 µg equiv/g, respectively, at 8 hours post-dose), large intestine contents (5.141 µg equiv/g at 8 hours post-dose), small intestine and small intestine contents (1.162 and 7.285 µg equiv/g, respectively, at 3 hours post-dose), adrenal gland (2.424 µg equiv/g at 3 hours post-dose), urinary bladder contents (4.761 µg equiv/g at 1 hour post-dose), liver (1.453 µg equiv/g at 1 hour post-dose]), renal cortex (1.266 µg equiv/g at 10 minutes post-dose), and renal medulla (1.038 µg equiv/g at 1 hour post-dose). In blood, the highest concentration of drug-derived radioactivity was 0.404 µg equiv/g, observed at 10 minutes post-dose. The tissues with the lowest relative concentrations (≤ 0.04 µg equiv/g) at tmax were those of the CNS: the brain (cerebrum, cerebellum, and medulla), dorsal root

nerve, sciatic nerve, and spinal cord. For most tissues, elimination was not complete by 72 hours post-dose.

In a QWBA study in albino rats, [14C]ixazomib citrate (mean dose of 0.32 mg/kg [free acid] [approximately 45.0 µCi/kg], formulated in a solution of 0.9% saline) was administered once IV to 6 male Sprague-Dawley rats. Drug-derived radioactivity was widely distributed in the DRG and blood and retained to the last sampling time point. Tissue concentrations were similar between QWBA and LSC analysis, and between the DRG and blood at each time point. The highest concentration of drug-related radioactivity in the DRG and blood was observed at 1 hour post-dose (0.244 and 0.270 µg equiv/g, respectively). The concentration-versus-time profile in the DRG was similar to that in blood; all drug-related material in blood was ixazomib, as evidenced by the ratio of ixazomib concentration to total radioactivity, as analyzed by LC/MS/MS and LSC, respectively (ranged from 1.0 to 1.2 through 312 hours post-dose).

The PK of ixazomib after IV administration of ixazomib was evaluated in Sprague-Dawley rats, New Zealand white rabbits, beagle dogs, and cynomolgus monkeys using non-compartmental analysis. After a single IV dose in PK/pharmacodynamic studies, ixazomib demonstrated a low blood and plasma clearance and a moderate blood Vss (1.05 to 2.78 L/kg) in all nonclinical species evaluated. The concentration-versus time curve of ixazomib displayed a distinct biexponential profile, with a steep initial distribution phase and a long apparent terminal elimination half-life ($t_{1/2}$) > 24 hours in all species tested. Ixazomib had a higher clearance and a larger Vss in plasma than in blood, largely because of the RBC partitioning; however, plasma clearance was low in all nonclinical species tested.

In vitro studies with ixazomib showed that ixazomib is moderately to highly bound to plasma protein in mouse (88-92%), rat (93-95%), dog (92-96%), monkey (92-95%), and human (88-89%) plasma. No concentration- or species-dependent trends were observed. An additional study with [14C]ixazomib citrate (0.05-10 µM) shiwed that ixazomib is highly bound to plasma protein in mouse (85%), rat (89%), dog (83%), and human (94%) plasma. No concentration-dependent trends were observed.

Evaluation of the human *in vitro* plasma protein binding conducted with pre-dose plasma samples from patients with advanced solid tumours or MM showed a mean value of approximately 99% bound.

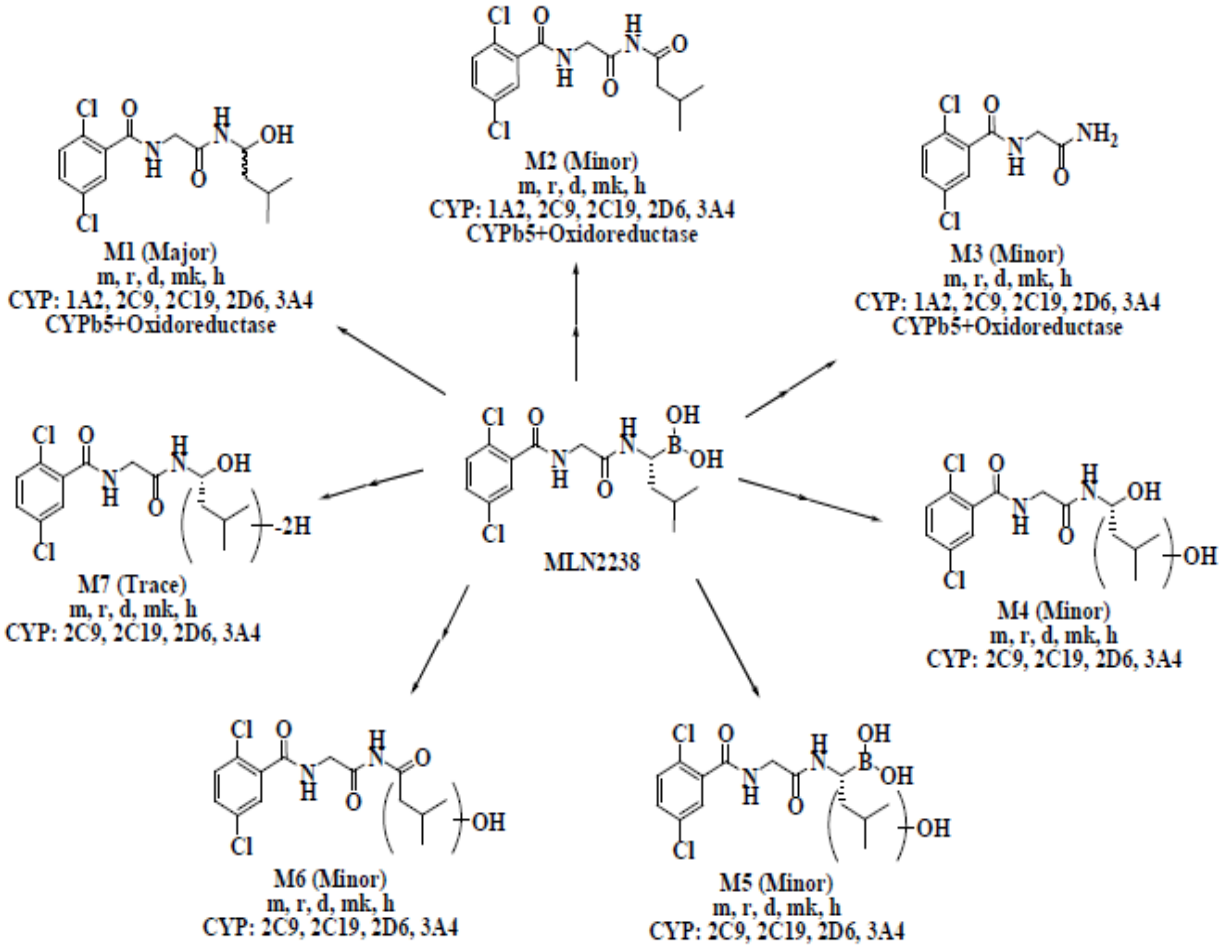
In vitro studies with ixazomib at concentrations of 0.1 and 1 µg/mL showed RBC partitioning in a concentration-dependent and saturable manner in mice, rats, dogs, monkeys, and humans. An additional *in vitro* RBC partitioning study using [14C]ixazomib citrate also showed that the distribution ratio of ixazomib-related substances into blood cells was moderate to high in mice, rats, dogs, and humans. As showen in a subsequent study, RBC partitioning of ixazomib was not affected by pre-treatment of blood samples with carfilzomib, a marketed selective proteasome inhibitor.

An *in vitro* study of transport of [14C]ixazomib citrate in human hepatocytes in the absence or presence of rifampin (200 µM) (a known OATP inhibitor) or cyclosporin A (10 µmol/L) (a known inhibitor of OATPs and sodium taurocholate co-transporting polypeptide [NTCP]), indicated that ixazomib is not a substrate of OATPs and NTCP.

Metabolism

Seven major metabolites of ixazomib (50 µM) were identified in hepatic microsomes (1 mg/mL) derived from male CD-1 mice, Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and humans (pooled, male and female); no metabolite unique to humans was identified *in vitro* (**Figure 2**).

Figure 2. Proposed Metabolic Pathways of Ixazomib in Mouse, Rat, Dog, Monkey, and Human Hepatic Microsomal Incubations and CYP Isozyme Mapping



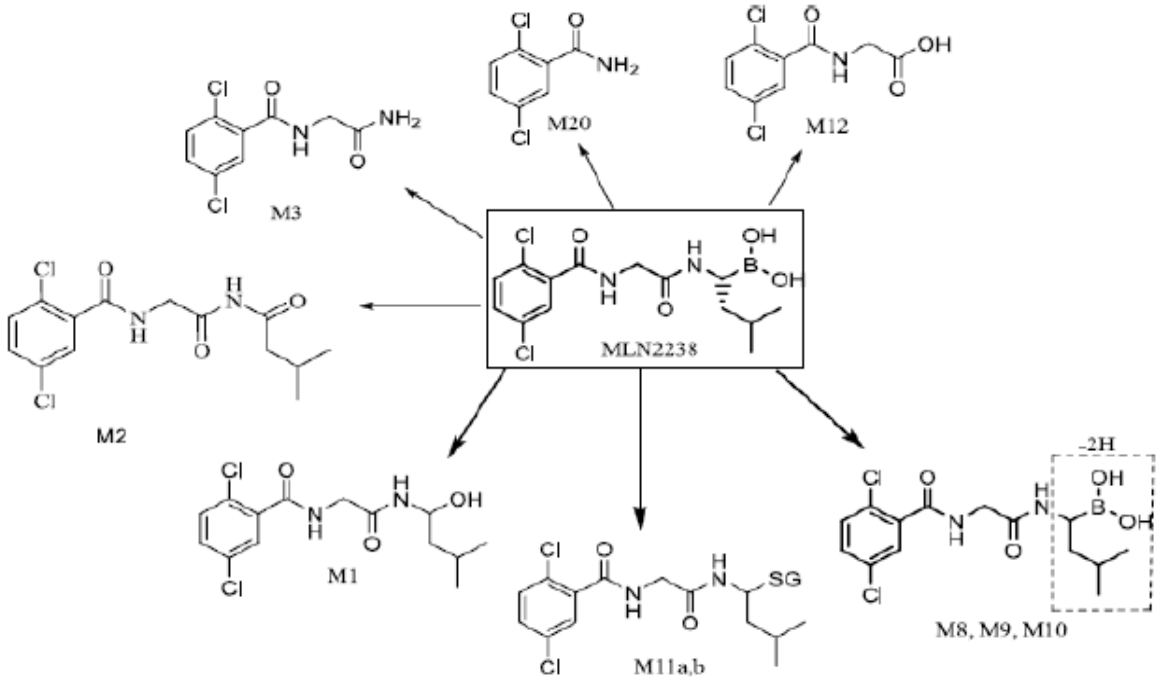
CYP = cytochrome P450; d = dog; h = human; m = mouse; mk = monkey; r = rat.
CYP isozymes, cytochrome b5, and oxidoreductase contributing to the metabolism of ixazomib and its metabolites are noted under each metabolite structure.

An additional *in vitro* metabolism study of [14C]ixazomib citrate using liver microsomes from male mice, male and female rats, male dogs, male monkeys, and humans (both males and females) also identified 7 metabolites of ixazomib (Report MLN9708-29687). Results showed that ixazomib was metabolized to M12, M3, M20, M1, M2, dehydrogenated ixazomib, UK-1, and others in the presence of a NADPH-generating system. M1 was the major metabolite in all species. There were no metabolites specific for HLMs.

The *in vitro* metabolism of [14C]ixazomib citrate (10 µg [rats and humans] and 100 µM [rats only]) was further evaluated in rat and human liver microsomes (1 mg/mL) and in cryopreserved rat and human hepatocytes (1 million viable cells/mL) (Report MIL-R1880R3). Liquid chromatography/ radiochromatograms of the metabolite profiles of [14C]ixazomib citrate in rat and human liver microsomes showed that [14C]ixazomib citrate was converted almost instantaneously to ixazomib.

In human liver microsomal extracts, M1 was the major metabolite, followed by M3, while M2, M8, M12, M15, M19, and M20 were observed at lower levels; human hepatocyte incubations again showed M1 and M3 as the dominant metabolites, with M8 in small quantities. Although M1 and M3 were the predominant metabolites in both microsomes and hepatocytes from rats and humans, neither of these metabolites was observed in human plasma samples.

Figure 3. Proposed Primary Metabolites of [14C]Ixazomib Citrate Identified in Rat and Human Liver Microsomes and Hepatocytes



The structures of metabolites M13 through M19 are tentative and are not shown in this figure.

The metabolism of [14C]ixazomib citrate was evaluated after a single PO dose of 0.8 mg/kg

[14C]ixazomib citrate to intact and BDC male Sprague-Dawley rats (Report MIL-R1800R2). Metabolite profiles of [14C]ixazomib citrate in plasma, urine, bile, and faeces were determined by HPLC with radioactivity detection and by LC/UV/MS. Radiochromatograms from analysis of pooled plasma, bile, and urine samples indicated that [14C]ixazomib citrate underwent moderate to extensive metabolism in rats; [14C]ixazomib citrate was immediately hydrolyzed to ixazomib and was not detected in any sample.

In plasma, ixazomib was found to be a major radioactive peak at all time points, representing 47.3% of the total radioactivity in plasma. M10 (23.5%) was the most predominant metabolite. Other metabolites observed were M1 (2.7%), M8 (5.7%), M9 (2.0%), M12 (5.3%), M13 (hydroxylated M1) (2.4%), and M14 (structure unknown) (11.2%).

In urine, of the 18.2% of the total dose excreted over 48 hours, ixazomib was a minor component compared to its metabolites, comprising less than 1% of the total dose administered. Metabolites M1, M8, M10, M12, M13, and M20 comprised 1.5%, 3.9%, 0.7%, 4.2%, 3.5%, and 3.0% of the total dose excreted in urine, respectively; interestingly, M20 was not observed in the urine collected from 0 to 6 hours, even though it was found to be a major component in later samples. In bile, M8 and M11 were the major drug-related components through 48 hours post-dose, comprising less than 4% and 3% of the total dose administered, respectively.

In faeces through 48 hours post-dose, ixazomib comprised 26.8% of the total dose administered, while metabolites M12 and M20 comprised 4.6% and 12.7% of the total dose administered, respectively.

Metabolite profiles were evaluated after single PO administration of [14C]ixazomib citrate at a dose of 0.2148 mg/kg (0.15 mg/kg as ixazomib) to male dogs. In plasma, ixazomib represented 58.2% of the total radioactivity. Additional metabolites comprised the remainder (41.8%) of the total radioactivity. In the urine and faeces during 0 to 120 hours, ixazomib comprised 3.1% of the urinary radioactivity and unidentified metabolites comprised the remaining 96.9% of the urinary radioactivity. Ixazomib comprised 23.9% of the faecal radioactivity and unidentified metabolites comprised the remaining 76.1% of the faecal radioactivity.

The metabolism of ixazomib citrate in humans was evaluated after PO administration of 2-mg/m^2 ixazomib (dosed as ixazomib citrate) to 3 subjects on Days 1, 4, 8, and 11 during a 21-day treatment cycle in Study C16003. Plasma samples, obtained after dosing on Days 1 and 11 and pooled, were used for preliminary metabolite identification and were analyzed by LC/MS/MS.

Ixazomib citrate rapidly converted to ixazomib, and unchanged ixazomib was the major drug-related component observed in Day 1 and Day 11 human plasma. Using mass spectral multiple-reaction monitoring (MRM) for potential metabolites that had been identified in rats and *in vitro* in human hepatocytes or liver microsomes only 1 metabolite, M8, was present in appreciable (about 10% of parent, by comparison of AUC8) levels in human plasma. Other metabolites previously identified in rat plasma or HLMs or human hepatocytes were not detected in human plasma.

All metabolites found in HLM studies were also found in rat and dog liver microsomal studies, supporting the use of rats and dogs as appropriate species for toxicology studies.

In a non-GLP-compliant study to evaluate the stability of ixazomib and ixazomib citrate (2 µM) in Sprague-Dawley rat and human serum and deproteinated serum, ixazomib or ixazomib citrate were spiked separately into rat and human serum and deproteinated serum.The results indicated that ixazomib citrate had converted to ixazomib in all test matrices, and that ixazomib was stable in rat and human serum and unstable in deproteinated rat and human serum. Changes in pH did not affect stability of ixazomib, and were likely not the reason for the instability in deproteinated rat and human serum.

Incubations with a panel of human complementary deoxyribonucleic acid (cDNA)-expressed recombinant CYP supersomes (about 100 pmol/mL) showed that all 5 major CYP isozymes (CYP1A2, 2C9, 2C19, 2D6, and 3A4), as well as cytochrome b5 and oxidoreductase, extensively metabolized ixazomib to M1 and, to a lesser extent, M2 and M3 (Report RPT-01136). The other oxidative metabolites, M4, M5, M6, and M7, were also detected with all CYP isozymes tested, except CYP1A2.

Ixazomib (50 µM) was metabolized by all of CYP-expressing microsomes; M1 was the main metabolite formed by all of CYP-expressing microsomes and other metabolites were also formed in minor extent. M12 and UK-1 were mainly formed by CYP2C19 and M2 was mainly formed by CYP3A4. M3, M20, and dehydrogenated ixazomib were formed by all of the CYP-expressing microsomes.

To determine the relative contributions of CYP1A2, 2C9, 2C19, 2D6, and 3A4 to the microsomal metabolism of ixazomib, selective CYP isozyme inhibitors were incubated with HLMs (0.5 mg/mL) and [14C]ixazomib (10 µM) at 37^0C. Metabolite amounts quantified with the online radiometric detector showed that CYP3A4 (34%) was the major CYP isozyme that contributed to the metabolism of ixazomib, followed by CYP1A2 (30.7%), 2D6(14.7%) , and 2C9(12.1%); the relative contribution of CYP2C19 was negligible.

The contribution of 7 CYP isozymes, including CYP3A4 and CYP1A2, to ixazomib metabolism was further evaluated using human cDNA CYP-expressing recombinant microsomes (Supersomes) (rCYPs)). At the 10-µM substrate concentration, CYP3A4 was the major CYP isozyme contributing to the metabolism of ixazomib, followed by CYP1A2 and then CYP2B6. The relative contributions of the 7 major CYP isozymes were: 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%) and 2C9 (1%). These data are similar to the results using chemical inhibitors of five CYP isozymes in HLMs at a 10-µM substrate concentration in a previous study.

Examination of the rate of formation of the measurable metabolites and the rate of disappearance

of ixazomib at 0.1 and 0.5 µM showed that there is little difference between the rates of metabolism of ixazomib in control incubations and in rCYP isozyme incubations.

Induction of CYP1A2, 2B6, and 3A4/5 activity by ixazomib citrate was examined *in vitro* in a non-GLP-compliant study by evaluating isozyme activity. Incubation with up to 5000-ng/mL (9.67 µM) ixazomib citrate resulted in 60%, 67%, and 73% decreases in CYP1A2, 2B6, and 3A4/5 activity, respectively, with corresponding decreases in CYP isozyme immune-reactive protein levels. The cause of these decreases in CYP isozyme activity and protein levels are unknown, but may be a result of cytotoxicity corresponding to prolonged exposure to ixazomib citrate in cultured human hepatocytes, as evidenced by an apparent concentration-dependent increase in lactate dehydrogenase (LDH) release resulting from deteriorating cell membrane integrity.

Ixazomib was evaluated as a reversible inhibitor of CYP isozyme activity in a study where HLMs (0.25mg/mL) from a pool of 200 individuals were incubated with marker substrates at concentrations approximately equal to their apparent Km. Incubation was performed in the presence or absence of ixazomib and known CYP inhibitors at various concentrations through a direct inhibition assay. There was little or no direct inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 by ixazomib in HLMs. The IC50s for these isozymes were reported as > 30 µM, the highest concentration of ixazomib examined. Assuming the potential inhibition by ixazomib of CYP isozymes would be competitive in nature, the Ki was assumed to be greater than 15 µM. Similar results were also observed in additional *in vitro* studies.

Excretion

After PO administration of [14C]ixazomib citrate to rats, the majority of the total radioactivity (the parent and its metabolites) was recovered in faeces. Similarly, in BDC rats, a substantial excretion of radioactivity was recovered in faeces after PO dosing, suggesting the possibility of unabsorbed compound or active intestinal secretion; urinary and biliary excretion of radioactivity accounted equally (22% to 23% of dose in 72 hours). After PO administration of [14C]ixazomib citrate to dogs, ixazomib citrate-related substances were excreted into the urine and faeces in comparable levels. In a separate study with unlabeled ixazomib, urinary excretion of the unchanged drug was negligible (< 5% of dose) after IV dosing.

After a single IV dose of [14C]ixazomib to Sprague-Dawley rats in a QWBA study the highest concentrations were primarily found in the gastrointestinal (GI) tract tissues and contents, urinary

bladder contents, renal cortex and medulla, and liver. After IV administration of ixazomib to Sprague-Dawley rats (0.3 mg/kg; n =4), beagle dogs (0.2 mg/kg; n = 3), and cynomolgus monkeys (0.1 mg/kg; n = 3), only a trace amount (< 5% of the dose) of ixazomib was excreted in urine.

2.3.4. Toxicology

Single dose toxicity

Table 7. Single-Dose Toxicology Studies of Ixazomib

Test Article Administered	Dose Route	Number/ Sex/Group	Dose (mg/kg)	Observation Period	GLP
CD-1 mice					
Ixazomib citrate	Oral gavage	11/M	2, 4, and 8[a]	24 hours	No
Sprague-Dawley rats					
Ixazomib	Oral gavage	3/M	0.1, 0.3, or 1	8 days	No
Ixazomib	IV injection	6/M	0.1, 0.3, 1, or 3	8 days	No
Ixazomib	IV injection	3/F	0 or 0.3	8 days	No
Beagle dogs					
Ixazomib citrate	Oral gavage	2/M	0.021, 0.07, 0.14, and 0.21[a, b]	8 days	No
Ixazomib	IV infusion	1/M; 3/M	0.1, 0.3, and 0.6	7 days	No

F =female(s); GLP = Good Laboratory Practice; IV = intravenous(ly); M = male(s).
a Doses are presented in terms of ixazomib.

b The same animals dosed at 0.021 mg/kg were dosed at 0.14 mg/kg after a 7-day washout period.

Single-Dose Toxicology Study of Ixazomib Citrate in Mice (Report MLN9708-24954)

Eleven male CD-1 mice/group were dosed with ixazomib citrate via a single oral gavage administration at 2, 4, or 8 mg/kg (doses in terms of ixazomib), dissolved in water for injection. TK analysis was conducted at 24 hours post-dose. Macroscopic and microscopic evaluations were not performed.All animals at 8-mg/kg showed adverse clinical signs at 6 hours post-dose, necessitating euthanasia (decrease in locomotor activity, hypothermia, and moribundity). No treatment-related effects were noted at 2 and 4 mg/kg. Between 2 and 4 mg/kg, Cmax and AUC from the time 0 to 24 hours (AUC24) increased in a dose-dependent. In conclusion, 4 mg/kg (mean plasma AUC24 = 926 hr*ng/mL) of ixazomib was the MTD under the conditions of this study; a single dose of 8 mg/kg resulted in moribundity and adverse clinical signs requiring euthanasia.

Single-Dose Oral Toxicology Study of Ixazomib in Rats (Report RPT-01104)
Three male Sprague Dawley rats per group were dosed via oral gavage with ixazomib at 0.1, 0.3, or 1 mg/kg, formulated in 10% hydroxypropyl-beta-cyclodextrin. All animals were euthanized on Day 8, and a complete macroscopic evaluation was performed. Toxicokinetic analysis was not performed in this study. All rats survived to scheduled euthanasia. Test article-related effects were limited to the 1mg/kg group, and included decreased activity (Days 1 to 3), decreased body weight gain (Days 1 to 4), decreased defecation (Days 2 to 4), soft stool (Days 1 and 2), and body surface staining (Days 1 to 3). No findings were reported during macroscopic evaluation. On the basis of these findings, the MTD of ixazomib in Sprague-Dawley rats after a single oral gavage administration was 1 mg/kg.

Single-Dose Oral Toxicology Study of Ixazomib Citrate in Dogs (Report MLN9708-24700)

Two male Beagle dogs per group received 0.021, 0.07, 0.14, and 0.21 mg/kg ixazomib citrate (doses in terms of ixazomib) via oral gavage, formulated in 0.5% weight-to-volume ratio methylcellulose; the same animals dosed at 0.021 mg/kg were dosed at 0.14 mg/kg after a 7-day washout period. Macroscopic and microscopic examinations were not performed. All animals survived to scheduled euthanasia. Both Cmax and AUC24 increased in a dose-dependent manner. After dosing at 0.14 mg/kg, time to reach Cmax (tmax) was slightly delayed because there were bimodal peaks of plasma concentrations; the cause of this could not be determined. No test article-related effects on body weight, food consumption, or ECGs were observed at any dose level. Possible test article-related effects were limited to loose stool and/or diarrhoea observed at 0.21 mg/kg, but these effects were not considered adverse because of the sporadic nature and lack of correlative findings. On the basis of only minor clinical findings, the MTD under the conditions of this study was considered to be 0.21 mg/kg (mean plasma AUC24 = 2140 hr*ng/mL).

Repeat dose toxicity

Table 8. Non-pivotal studies

Species/ Strain / Report	**Method of administration (vehicle / Formulation)**	**Duration of dosing**	**Dose (mg/kg)**	**Number and sex per group**	**NOEL (mg/kg)**	**Noteworthy findings:**
Rat/ Sprague Dawley (RPT-01130)	PO (10% HP-ß-CD/2.8% mannitol	11 days (1 Cycle) Days 1,4,8,11	0.3, 0.6, 1.0	Males, 5/group main study +3/group TK	0.3 MTD 1.0	Mortality: None. Clinical signs: At 1.0 mg/kg: decreased defecation, soft stools, body surface staining. BW: At 0.6 and 1.0 mg/kg: decreased BW on Day 7. Haematology: At 0.6 mg/kg: On Day 12: increased absolute NEUT. At 1.0 mg/kg: On Day 12: increased WBC count and absolute NEUT, decreased PLT. Serum Chemistry: At 0.6 mg/kg: On Day 12: increased ALT, AST, SDH, and glucose. At 1.0 mg/kg: On Day 12: increased glucose. Organ weights: At 0.6 and 1.0 mg/kg: decreased thymus weight. At 1.0 mg/kg: decreased spleen weight, increased liver weight. Macroscopic examination: At 0.6 and 1.0 mg/kg: small thymus. Microscopic examination: At 0.6 and 1.0 mg/kg: small and large intestine mucosal hyperplasia and neutrophilic infiltrates; thymus cortical lymphoid depletion; spleen sinusoidal neutrophilic leukocytosis; mesenteric lymph node lymphoid necrosis and neutrophilic infiltrates; and bone marrow hypocellularity. At 1.0 mg/kg: luminal distension of the stomach and small intestine. Day 11 plasma TK: At 0.3 mg/kg: Cmax 9.38 ng/mL, AUC24 204 hr*ng/mL. At 0.6 mg/kg: Cmax 25.9 ng/mL, AUC24 480 hr*ng/mL.
Dog/ Beagle/	PO (10%	QD x 7 days (1	0, 0.05,	Males; 3/group	0.10	Mortality: At 0.20 mg/kg: 1 dog on Day 6.

KLA00345	HP-ß-CD/ 2.8%mannitol)	cycle)	0.1, 0.2			Clinical observations: At 0.20 mg/kg:[a] vomiting, mucoid faeces. Neurological observations: At 0.20 mg/kg:[a] ataxia, difficulty repositioning limbs, low arousal, and posture of lying on side. BW: At 0.20 mg/kg:[a] decreased 0.5 kg between Days 1 and6. Haematology and serum chemistry: Numerous alterations only observed in the animal euthanized on Day 6; the majority were associated with dehydration, inflammation, or moribundity. Coagulation: At 0.20 mg/kg: increased FIB in 1 animal surviving until the end of the study. Macroscopic examination: At 0.20 mg/kg:[a] stomach and intestinal multiple foci of mucosal congestion and/ or haemorrhage. Microscopic examination: At 0.20 mg/kg: intestinal marked lymphoid necrosis in Peyer's patches[a] and submucosal lymphoid nodules; mesenteric lymph node[a] marked germinal center lymphoid necrosis, follicular and paracortical lymphoid depletion, and moderate capsular neutrophilic infiltrates; sympathetic ganglia (abdominal and thoracic), colonic myenteric plexus[a], and DRG minimal to moderate chromatolysis and cytoplasmic accumulations of eosinophilic granular material; thymic[a] moderate to marked cortical lymphoid necrosis and depletion, small intestine lamina propria minimal to mild lymphoid necrosis and superficial crypt abscess; cecal minimal to mild glandular abscess, mucosal congestion, and haemorrhage; altered hematopoiesis[a], liver[a] minimal cholestasis and hepatic necrosis; renal[a] minimal tubular epithelial single-cell necrosis; adrenal[a] minimal cortical neutrophilic infiltrates and single-cell necrosis; parathyroid[a] mild chief cell atrophy; prostate[a] mild glandular epithelial single-cell necrosis. Day 1 plasma TK: At 0.05 mg/kg:[b] Cmax 11.1 ng/mL, AUC24 118 hr*ng/mL. At 0.10 mg/kg: Cmax 51.2 ng/mL, AUC24 193 hr*ng/mL. At 0.20 mg/kg: Cmax 48.4 ng/mL, AUC24 283 hr*ng/mL. At 0.05 mg/kg: Cmax 37.5 ng/mL, AUC24 357 hr*ng/mL. At 0.10 mg/kg: Cmax 71.8 ng/mL, AUC24 613 hr*ng/mL. At 0.20 mg/kg:[c] Cmax 104 ng/mL, AUC24 787 hr*ng/mL.

a Findings were only observed in the animal euthanized on Day 6.
b n=2 (1 animal had no exposure through all time points and was excluded from mean calculations)
c n=2 (1 animal died before day 7)

Table 9. Overview of Pivotal Repeated Dose Toxicity Studies Conducted using the Oral Route of Administration

Report	Species	Duration of dosing	Test article	Route
KLA00354 and KLA00354 Amendment 1	Sprague Dawley Rat	1 month (2 cycles)*	Ixazomib	Oral gavage

WIL-416104, WIL416104 Amendment 1 and WIL-416104 Amendment 2	Sprague Dawley Rat	3 months (5 cycles)*	Ixazomib citrate	Oral gavage
WIL-416165	Sprague Dawley Rat	6 months (7 cycles)*	Ixazomib citrate	Oral gavage
KLA00385 and KLA00385 Amendment 1	Beagle dog	2 weeks	Ixazomib	Oral gavage
WIL-416105, WIL-416105 Amendment 1 and WIL-416105 Amendment 2	Beagle dog	3 months (5 cycles)*	Ixazomib citrate	Oral gavage
WIL-416164	Beagle dog	9 months (10 cycles)*	Ixazomib citrate	Oral gavage

- *One-Month (2-Cycle) Intermittent-Dose Oral Toxicology Study of Ixazomib (Report KLA00354)*

A GLP-compliant intermittent-dose study in male and female Sprague-Dawley rats was conducted to evaluate the potential toxicity and TK of ixazomib when administered by oral gavage for 2 cycles over 32 days. Each cycle consisted of BIW dosing for 2 weeks separated by a 10-day non-dosing period. Cycle 2 was followed by a 14-day recovery period. Rats received either vehicle (55-mM citrate and 1% propylene glycol, pH 5.2) or ixazomib at 0.4, 0.8, or 1.2 mg/kg. A single dose of 1.2 mg/kg was not tolerated; surviving males were not dosed further during Cycle 1 and the dose was lowered to 1.0 mg/kg during Cycle 2. High-dose females received a single dose of 1.0 mg/kg during Cycle 1; however, as a result of the lack of tolerability, remaining high-dose females were not dosed for the remainder of the study.

Each group was assigned 15 animals per sex (10 main study and 5 recovery), with an additional 3 rats/sex in the vehicle control group and 9 rats/sex/group in the ixazomib groups for TK analysis. After the 2 cycles of dose administration, up to 10 main study rats/sex/group were euthanized on Day 33, and the remaining recovery rats (up to 5/sex/group) were euthanized on Day 47 after a 14-day recovery period. All surviving high-dose females were euthanized on Day 33 because dosing was discontinued after Day 1.

Plasma exposure to ixazomib, as measured by Cmax and AUC24, increased in an approximately dose-proportional manner at all doses and was generally similar between males and females. There was also no accumulation over the course of the study.

There were a total of 20 deaths (died or were euthanized in moribund condition) over the course of the study. Several of the deaths occurred after TK blood collection, including in 2 control rats. These deaths were presumably related to blood collection procedures, but the deaths in the ixazomib-treated animals may have been related to test article administration. Of those animals euthanized in moribund condition, the cause was attributed to metabolic stress, likely precipitated by intestinal mucosal toxicity (acute inflammation, oedema, mucosal thickening, and lamina propria cellular depletion) and associated fluid and electrolyte imbalances. In addition, minimal to moderate bone marrow cellular depletion, minimal to moderate cortical cellular necrosis of the thymus and adrenal gland, mild to moderate vacuolation of the adrenal gland, mild cellular depletion of the thymus, and minimal to moderate lymphoid depletion of the spleen, Peyer's patches, and/or mandibular and mesenteric lymph nodes were also observed. Clinical signs before death were also consistent with a GI disturbance (mucoid and soft faeces) and stress (hunched posture, urine and porphyrin staining). Minimal to moderate hepatocellular vacuolation was observed in many of these animals; minimal to mild necrosis of the liver in a few of these animals was considered secondary to moribundity and not a primary test article-related effect.

At all doses (0.4, 0.8, and 1.2/1.0 mg/kg), there were GI tract and adrenal adverse findings that were generally dose dependent in incidence or severity. Gastrointestinal changes included minimal to mild intestine mucosal thickening and/or minimal to mild acute inflammation. Macroscopically, distended stomach was also observed at all doses, but this is a common toxicity finding and is not necessarily specific for GI toxicity. Clinical pathology changes that may have been related to GI effects included decreased ALT, AST, alkaline phosphatase (ALP), blood urea nitrogen (BUN), and cholesterol (not all of these parameters were decreased at all doses and/or in both sexes). In addition, there were increases in WBCs, neutrophils, monocytes, and fibrogen that were consistent with an inflammatory response (potentially related to GI tract findings), as well as increases in basophils and decreases in eosinophils. Decreased body weights and food consumption at 0.8 and 1.2/1.0 mg/kg, and soft faeces, porphyrin staining, urine staining, and rough hair coat observed at 1.2/1.0 mg/kg were also likely reflective of GI tract toxicity. Minimal to mild adrenal gland cortical vacuolation was also observed at all doses and correlated with increased relative adrenal gland weights in males at 0.8 and 1.2/1.0 mg/kg. Increased liver weights (absolute and relative to body) were also noted at all doses, but without a microscopic correlate.

At 0.8 and 1.2/1.0 mg/kg, there were lymphoid system and bone marrow effects that included minimal to moderate mesenteric and mandibular lymph node lymphoid depletion, minimal to marked thymic cortical cellular depletion, minimal to mild lymphoid depletion of the Peyer's patch, and, in bone marrow smears, increased total myeloid cell counts and myeloid:erythroid ratio (M:E) and decreased lymphocyte count compared to controls. Macroscopic correlates included small thymus and decreased thymic weights (absolute and relative to body).

- *Three-Month (5-Cycle) Intermittent-Dose Oral Toxicology Study of Ixazomib Citrate (Report WIL-41610)*

The potential systemic toxicity and TK of ixazomib was evaluated when administered as ixazomib citrate by oral gavage to male and female Sprague Dawley rats for 5 cycles over 94 days. Each cycle consisted of BIW dosing for 2 weeks separated by a 10-day non-dosing period. Cycle 5 was followed by a 14-day recovery period. Rats received either vehicle or ixazomib citrate at 0.2, 0.4, and 0.8 mg/kg (doses in terms of ixazomib) in Cycles 1 and 2; before initiation of Cycle 3, the 0.8 mg/kg dose was reduced to 0.6 mg/kg. Each group was assigned 15 animals per sex (10 main study and 5 recovery [with the exception of the 0.2-mg/kg dose group, which had 10/sex]), with an additional 6 rats/sex in the vehicle control group and 18 rats/sex/group in the test article-dosed groups for TK analysis. After the 5 cycles of dose administration, up to 10 main study rats/sex/group were euthanized on Day 95, and the remaining recovery rats (up to 5/sex/group) were euthanized on Day 109 after a 14-day recovery period.

After administration of 2 cycles of 0.8-mg/kg, 1 male and 1 female were euthanized in moribund condition on Days 29 and 31, respectively, as a result of clinical signs that included hypoactivity, dermal atonia, thin appearance, pale extremities, extremities and/or body cool to the touch, labored respiration, decreased defecation, and smaller than normal faeces. Microscopic findings contributing to the condition of these animals included minimal to moderate GI epithelial degeneration, minimal to mild intestinal epithelial single-cell necrosis, minimal to mild intestinal acute inflammation, mild bone marrow hypocellularity/single-cell necrosis, and/or mild to moderate lymphoid depletion that predisposed these rats to possible sepsis. Three additional animals were found dead; 2 of the 3 deaths were vehicle control animals (1 male and 1 female each) and hence were unrelated to test article administration (related to gavage or blood collection procedural injury). The third animal, a female at 0.8/0.6 mg/kg, was found dead shortly after clinical pathology blood collection on Day 95. This animal had been dosed for a full 5 cycles and showed microscopic findings of mild to moderate epithelial

hyperplasia in the small intestines and moderate lymphoid depletion and minimal single-cell necrosis in the mesenteric and/or popliteal lymph nodes. This death was considered related to blood collection procedures but could not be definitively determined as unrelated to test article administration.

In animals surviving to the end of the study, there were no test article-related clinical observations, ophthalmic or macroscopic findings, or alterations in coagulation parameters at any dose level.

At all dose levels, test article-related microscopic findings at the main study necropsy were observed in the GI tract and lymph nodes. Findings in the GI tract included minimal to mild epithelial hyperplasia, minimal acute inflammation and single-cell necrosis in the small intestine at all doses, and at 0.8/0.6 mg/kg, minimal epithelial hyperplasia and acute inflammation of the rectum. Haematology changes that generally correlated with GI tract inflammation included increased circulating leukocyte, neutrophil, lymphocyte, monocyte, and/or basophil counts at ≥ 0.2 mg/kg. Decreased food consumption at ≥ 0.4 mg/kg and decreased weight gain in males at 08/0.6 mg/kg were also likely related to the GI tract injury, and may have contributed to decreased cholesterol and K. Minimal to moderate lymphoid depletion of the mandibular and mesenteric lymph node and/or Peyer's patches, and minimal to mild single-cell necrosis in the lymph nodes were also observed at all doses. Decreased eosinophil and platelet counts at ≥0.4 mg/kg were likely related to lymphoid depletion. In general, all findings were reversed or reversing by the end of the 14-day recovery period.

- *Six-Month (7-Cycle) Intermittent Dose Oral Toxicology Study of Ixazomib Citrate (Report WIL-416165)*

A GLP-compliant intermittent-dose study in male and female Sprague-Dawley rats was conducted to evaluate the potential systemic toxicity and TK of ixazomib, when administered as ixazomib citrate, by oral gavage for 6 months (7 dosing cycles). Each cycle consisted of 3 QW doses separated by a 13-day non-dosing period (28-day cycle). Cycle 7 was followed by a 14-day recovery period. Rats received either vehicle (55-mM citrate buffer and 0.45% NaCl in SWI, USP, pH 5.8) or ixazomib citrate at 0.2, 0.4, and 0.8 mg/kg (doses in terms of ixazomib). Each group was assigned 15 rats/sex (10 main study and 5 recovery). Starting with Cycle 3 (Day 56), the dose level for the high-dose females was lowered from 0.8 to 0.6 mg/kg as a result of the overt toxicity and mortality (referred to hereafter as the 0.8/0.6-mg/kg group).

A total of 7 high-dose female deaths occurred. Two high-dose (0.8 mg/kg) females died after the first dose (Days 1 and 2); these animals were subsequently replaced because their mortality was considered not clearly test article related at that time. Four females (0.8 mg/kg) died between Days 9 and 36, and a fifth female (0.8/0.6 mg/kg) was found dead on Day 170. All 7 animals were found dead within 2 days of dose administration. Clinical observations in these early death animals included red material around nose, yellow material around the urogenital area, and clear discharge from both eyes. The mortality observed in females may have been related to greater Cmax in high-dose females relative to that in males, or the age of the rats at the start of the study (7 weeks old), which was younger than in previous rat studies. For animals where a cause of death could be determined, the early death was attributed to a combination of test article-related intestinal, liver, and/or lymphoid toxicity. Test article-related microscopic observations in the intestines included minimal to mild neutrophilic infiltrates in the lamina propria, minimal to mild epithelial hyperplasia and necrosis, and mild villous atrophy. Test article-related changes in the liver included mild to moderate hepatocellular degeneration/necrosis, moderate generalized hepatocellular vacuolation, and minimal neutrophil infiltration in the sinusoids. Minimal to moderate lymphoid depletion and/or necrosis was observed in the lymphoid tissues, and minimal to mild hypocellularity and/or minimal single cell necrosis was observed in the bone marrow.

There was also a loss of medullary plasmacytosis in the submandibular lymph nodes of the early mortality females. Additional test article-related microscopic findings in the early mortality females were mild haemorrhage and minimal to mild degeneration/necrosis of the adrenal zona fasciculata; minimal to mild depletion of cytoplasmic secretory granules and single-cell necrosis of the cells of the adrenal medulla; and mild ulceration and minimal degeneration/necrosis of muscle of the tongue.

At all doses, there were generally dose-dependent GI tract effects that included minimal to moderate epithelial hyperplasia, minimal to mild neutrophilic infiltrates, and minimal single-cell necrosis in the lamina propria of the small and large intestines. The GI tract findings at 0.2 mg/kg were all generally minimal in nature. At ≥ 0.4 mg/kg, GI tract findings also included increased mandibular salivary gland mucin, minimal to moderate sub-acute inflammation of the glandular and nonglandular stomach, and, at 0.8/0.6 mg/kg, minimal to mild erosions of the glandular stomach and ulceration of the non-glandular stomach. Gastrointestinal changes correlated with higher absolute values for WBCs, neutrophils, lymphocytes, monocytes, and basophils (males only) at ≥ 0.4 mg/kg. Body weight changes also tended to correlate with GI tract effects; by the end of the dosing period, 0.4-mg/kg males had a 3.8% reduction (relative to controls) in body weight gain, while 0.8/0.6-mg/kg males and females had an 11.1% and 10.1% reduction in body weight gain, respectively. Clinical observations that also correlated with GI tract findings included diarrhoea, small/soft/decreased faeces, hypoactivity, thin appearance, and yellow material around the urogenital and anogenital areas and forelimbs in 0.8/0.6-mg/kg males and females. All of the GI tract and related findings were reversed or reversing after the 2-week recovery period.

Lymphoid effects were also noted at ≥0.2 mg/kg and consisted of generally dose-dependent increased incidence of minimal to mild mesenteric lymphoid necrosis that in males was also characterized by lymphoid depletion. The lymphoid findings at 0.2 mg/kg were all generally minimal in nature. At ≥ 0.4 mg/kg, additional lymphoid findings included minimal to mild neutrophil infiltrates in the red pulp of the spleen and minimal bone marrow hypocellularity. Neutrophilic infiltrates correlated with higher circulating neutrophil counts at ≥ 0.4 mg/kg. All of the lymphoid and adrenal effects were reversed or reversing by the end of the recovery period.

Microscopic observations of uncertain relationship to the test article were observed in the endocrine system, reproductive tissues and blood vessels; these effects were: minimal to mild decreased vacuolation of the zona fasciculata of the adrenal cortex in all test article-treated male groups, increased lobulo-alveolar hyperplasia and increased secretion of the mammary gland in 0.8/0.6 mg/kg females, a single incidence of spermatid retention in the testis in one 0.8/0.6 mg/kg male, and minimal mononuclear perivasculitis of the meninges of the brain and spinal cord and the submucosa of the intestine in one 0.8/0.6 mg/kg male. Clear discharge from the eyes and red material around the nose and mouth in 0.8/0.6 mg/kg males and females and red material around the nose were clinical observations that were not clearly related to any other finding and were not observed during the recovery period. None of these uncertain drug-related microscopic findings were observed after the 2-week recovery period.

- *Two-Week (1-Cycle) Intermittent-Dose Oral Toxicology Study of Ixazomib (Report KLA00385)*

A GLP-compliant intermittent-dose study in male and female beagle dogs was conducted to evaluate the potential toxicity and TK of ixazomib when administered by oral gavage BIW for 2 weeks. The single dosing cycle was followed by a 14-day recovery period. Dogs received either vehicle (55-mM citrate and 1% propylene glycol, pH 5.2) or ixazomib in vehicle. High-dose males were administered 0.3 mg/kg, but demonstrated severe toxicity on Day 1 and therefore received no additional test article, but were allowed to recover for 25 days before necropsy (Day 26). Macroscopic and microscopic pathology evaluations were only conducted on surviving 0.3-mg/kg males that were allowed to

recover. The other male groups were dosed at 0.1 and 0.2 mg/kg, while the female dose groups were 0.1, 0.15, and 0.2 mg/kg. Each group was assigned 5 animals per sex, with 3 animals assigned to main study necropsy (Day 12) and 2 animals to recovery necropsy (Day 26).

Two males at 0.3 mg/kg were euthanized on Day 5 after having received a single dose, and 1 male at 0.2 mg/kg was euthanized on Day 9 after having received 2 doses. Dose-limiting toxicity in these animals was attributed to lymphoid tissue depletion and necrosis, and GI inflammation, ulceration, and enteropathy. Neuronal degeneration in peripheral autonomic ganglia (characterized by cell swelling, cytoplasmic chromatolysis with eosinophilic accumulations, and/or necrosis) may have contributed to functional GI effects. Additional findings in the 0.2 mg/kg male included arterial fibrinoid necrosis in multiple organs, and minimal axonal degeneration in the trigeminal tracts in the medulla of the brain and the dorsal spinal columns and/or dorsal spinal rootlets of the spinal cord. The axonal degeneration in the brain and spinal cord was considered a secondary effect of the injury to the peripheral ganglia and was characteristic of a primary sensory neuropathy. Clinical signs before death were also consistent with a GI disturbance (emesis; diarrhoea; and soft, mucoid with blood, and/or yellow or green faeces), dehydration, ataxia, decreased reflexes, and circulatory disturbances (petechiae and ecchymoses, erythema, and/or tachycardia), accompanied by decreased food consumption and body weight.

In surviving males given a single dose of 0.3 mg/kg, similar clinical observations were observed during the recovery period and included thin body condition, lethargy, dehydration, tacky mucous membranes, cardiac arrhythmia, diarrhoea, ataxia, wide-based gait in hind-limbs, and reduced withdrawal and extensor carpi reflexes. Increased platelets were also observed on Day 12 in the surviving 0.3 mg/kg animals.

There were no test article-related findings at 0.1 mg/kg, with the exception of minimal neuronal degeneration in the cervical DRG of 1 male and the lumbar DRG of another male. At ≥ 0.15 mg/kg, neuronal findings were also minimal in nature and included end organ ganglia degeneration in the salivary gland, stomach, ileum, cecum, colon, and/or rectum, and axonal degeneration of the dorsal column (in one 0.15-mg/kg female). Minimal neuronal degeneration of the sympathetic ganglia (thoracic and abdominal) was also noted at 0.2 mg/kg. In general, the microscopic nerve findings were minimal in severity, irrespective of dose, although there was a trend for either more affected locations or animals at the higher doses. Physical or neurological examination findings that correlated with neurotoxicity included ataxia and decreased extensor carpi reflexes in a few dogs at doses ≥ 0.2 mg/kg. Of note, lameness was noted in 1 female each at 0.1 and 0.15 mg/kg, but not at higher doses. All neuronal-related effects at ≤0.15 mg/kg were reversed or reversing by the end of the 2-week recovery period.

However, the neuronal injury at ≥ 0.2 mg/kg was still present after the 14 day recovery period, with neurological examination findings of ataxia, wide-based stance, and reduced extensor carpi reflex. In addition, nerve fibre degeneration in peripheral nerves and spinal cord/brain sensory tracts had a higher incidence or severity at the recovery necropsy; however, the timing, appearance, and location of this change were consistent with a primary effect in peripheral ganglia, which occurred during the dosing period, and secondary degeneration of associated nerve fibres during the recovery period. Microscopic findings observed at the recovery necropsy at ≥0.2 mg/kg included minimal neuronal degeneration in the cervical and/or lumbar DRG (along with minimal to mild degeneration of nerve fibres associated with the DRG) and sympathetic ganglia; and minimal to moderate axonal degeneration of the sciatic and/or sural nerves, dorsal column of the spinal cord, and trigeminal tract in the medulla of the brain.

Additional findings present at 0.2 mg/kg included GI tract and lymphoid effects. The GI tract findings were minimal or mild acute or subacute inflammation and congestion or haemorrhage of the intestines (males), as well as minimal chronic inflammation of the pylorus in 1 male. Microscopic GI findings correlated with the macroscopic findings of red discoloration of the ileum, cecum, colon, and/or rectum mucosa in males at ≥ 0.1 mg/kg. Lymphoid system effects were also noted at 0.2 mg/kg and included minimal lymphoid depletion in the Peyer's patches (1 female), minimal neutrophilic infiltration of the spleen (males), and minimal thymic cortical cell depletion (in males, which correlated with decreased absolute and relative to body thymus weights; decreased absolute and relative thymus weights were also observed in males at 0.1 mg/kg and females at 0.2 mg/kg, although these were without microscopic correlates). Minimal and/or mild erosion and inflammation of the tongue in males at 0.2 mg/kg may have been test article related, or may have been a result of gavage trauma. Clinical observations at 0.2 mg/kg consistent with GI tract injury included soft faeces and vomiting (males only). Increased fibrinogen, WBC, neutrophils, and monocytes at 0.2 mg/kg were also consistent with the GI tract inflammatory response. Decreased BUN (males only) and phosphorus (PHOS) may have also been related to GI tract injury. Intestinal and thymic effects were not clearly reversed after the end of the recovery period.

In males at 0.1 and 0.2 mg/kg, possible increases in QTc were observed at 1 to 2 hours after dosing on Day 11; however, these increases were not observed in females that had similar or higher exposures.

- *Three-Month (5-Cycle) Intermittent-Dose Oral Toxicology Study of Ixazomib Citrate (Report WIL-416105)*

Ixazomib citrate was administered by oral gavage for 5 cycles over 94 days. Each cycle consisted of BIW dosing for 2 weeks separated by a 10-day non-dosing period. Cycle 5 was followed by a 14-day recovery period. Dogs received either vehicle (55-mM citrate and 0.45% NaCl, in SWI, USP, pH 5.8) or ixazomib citrate at 0.05, 0.10, and 0.15 mg/kg (doses presented in terms of ixazomib). Each group was assigned 3 main study animals/sex; the control, 0.10 mg/kg, and 0.15 mg/kg groups each had an additional 3 recovery animals/sex/group. After the 5 cycles of dose administration, 3 main study animals/sex/group were euthanized on Day 95, and the remaining recovery animals (up to 3/sex/group) were euthanized on Day 109 after a 14-day recovery period.

There was no early mortality in any of the animals dosed with ixazomib. There were no test article-related changes in body weights, food consumption, organ weights, ophthalmic or ECG parameters, clinical pathology, or macroscopic observations at any dose level.

At ≥ 0.10 mg/kg, test article-related microscopic findings included minimal to mild neuronal degeneration of the sympathetic, dorsal root, peripheral autonomic (salivary gland), and end organ ganglia, and minimal secondary axonal/nerve fibre degeneration of the peripheral nerves and ascending tracts in the axonal and dorsal columns of the spinal cord. After the 14-day recovery period, the primary neuronal degeneration of the DRG and secondary effects observed in the peripheral nerves and spinal cord were reversed at 0.10 mg/kg and reversing at 0.15 mg/kg. An increased incidence of clear ocular discharge was also noted at ≥ 0.10 mg/kg.

- *Nine-Month (10-Cycle) Intermittent Dose Oral Toxicology Study of Ixazomib Citrate (Report WIL-416164)*

Ixazomib citrate was administered by oral gavage for 9 months (10 dosing cycles) followed by a 2-week recovery period. Dogs received either vehicle (55-mM citrate buffer and 0.45% NaCl in SWI, USP [pH 5.8]) or ixazomib citrate at 0.05, 0.10, and 0.20 mg/kg (doses in terms of ixazomib) for 10 cycles. Each cycle consisted of QW dosing for 3 weeks with each cycle separated by a 13-day non-dosing

period. Each group was assigned 3 main study animals/sex; the control, 0.10- and 0.20-mg/kg groups had an additional 3 recovery animals/sex. Main study animals were euthanized on Day 267, while recovery animals were euthanized on Day 280. Blood samples for TK analysis (Days 0, 14, 252, and 266) were collected from all animals.

All animals survived to the scheduled necropsies. There were no test article-related changes in body weight, food consumption, clinical observations, ECGs, neurobehavioral functional assessment, coagulation, or organ weights at the primary or recovery necropsies. There were also no test article-related changes in any parameter at 0.05 mg/kg.

At ≥0.10 mg/kg, ixazomib-associated effects in the GI tract and lymphoid tissue included minimal neutrophil infiltration in the stomach (predominantly in the pylorus) and intestines with neutrophil infiltration of the Peyer's patches in females and the mesenteric lymph node in males and females at 0.20 mg/kg, and minimal erosions in the stomach in males at 0.20 mg/kg. Neutrophil infiltration correlated with higher mean absolute counts for white blood cells, neutrophils, and monocytes at 0.20 mg/kg. After the 2-week recovery period, stomach erosions were not present and the neutrophil infiltration in the lymph nodes and intestine was reversed or reversing.

Neuronal findings were observed primarily at 0.20 mg/kg. These findings included neuronal degeneration of the sympathetic (celiac and stellate), dorsal root, and end organ (salivary gland) ganglia, and minimal secondary axonal/nerve fibre degeneration of the peripheral nerves (vagus and sciatic nerves, dorsal roots and mixed spinal nerves) and ascending tracts in the dorsal columns of the spinal cord, and in white matter tracts in the medulla oblongata of the brain (1 female only). Gliosis of the dorsal column of the spinal cord in 1 male and 1 female at 0.20 mg/kg and the white matter tracts in the brain of 1 female at 0.20 mg/kg was a secondary change to degeneration of the axons of the ascending tracts. At the end of the 2-week recovery period, nerve fibre degeneration of the DRG and an increase in axonal degeneration in the dorsal columns of the spinal cord were still present in males and females at 0.20 mg/kg. There were no microscopic changes noted in the brain or in the neurons of the peripheral ganglia (sympathetic, DRG, or end organ ganglia) in animals at the recovery necropsy.

Additional test article-related findings at 0.20 mg/kg included decreased absolute counts for lymphocytes (-26%) in females, increased aspartate aminotransferase (males only [36%]), and decreased serum phosphorus (-19% to -20%). There were no test article-related changes in haematology or serum chemistry at the recovery necropsy.

Genotoxicity

Table 10. Genotoxicity studies with ixazomib

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria/MBR08-152/GLP	Salmonella strains (TA98, TA100, TA1535, TA1537), Escherichia coli (WP2uvrA)	Ixazomib +/- S9 Confirmatory studies: up to 5000 ug/plate in strain TA98; up to 2500 ug/plate in strain WP2uvrA; up to 1000 ug/plate in strains TA1537 and TA1535; up to 500 ug/plate in strain TA100	Not mutagenic under the conditions of this study
Chromosomal aberrations *in vitro*/MBR12-367/GLP	human peripheral blood lymphocyte	Ixazomib citrate +/- S9 from 0.010 to 20 ug/mL (-S9) and from 0.10 to 50 ug/mL (+S9) for the 3-hour exposure; from 0.010 to 0.50 ug/mL (-S9) for the 22-hour exposure	Statistically significant increases in the % of cells with structural chromosomal aberrations in the 3-hour exposure (-S9) at 0.10 ug/mL ($p < 0.01$), in the 22-hour exposure (-S9) at 0.075 and 0.080 ug/mL ($p < 0.01$); in the 3-hour exposure

		were used during the chromosome aberration assay	(+S9) at 35 and 45 ug/mL ($p < 0.01$) and 40 ug/mL ($p < 0.05$). Statistically significant increases in the percentage of cells with > 1 aberration were noted after 22 hours (-S9) at 0.080 ug/mL ($p < 0.05$) and after 3 hours (+S9) at 45 ug/mL ($p < 0.01$). no statistically significant increases in polyploidy and endoreduplication
Chromosomal aberrations *in vivo*/WIL-416152/GLP	Male mouse, micronuclei in bone marrow	Ixazomib citrate definitive phase: single oral dose 2, 4, 8 mg/kg bone marrow collection between 24 and 28 hours and 44 and 48 hours postdose	no increase in the % number of micronucleated polychromatic erythrocytes compared to the vehicle group, and no bone marrow cytotoxicity (i.e., decrease in the ratio of polychromatic erythrocytes to total erythrocytes) was observed
DNA damaging potential MLN9708-24961/GLP	*In Vivo* Male Mouse Comet Assay	ixazomib citrate 2, 4, 6 mg/kg orally administered on 2 consecutive days: specimens from the liver and glandular stomach collected 24 hours after the first dose and 3 hours after the second dose	No statistically significant differences in % tail DNA were observed in either tissue between any of the test article-dosed groups and the vehicle control

Carcinogenicity

No carcinogenicity studies have been conducted with ixazomib (see discussion on non-clinical aspects).

Reproduction Toxicity

- *Study MLN9708-24960: Range-Finding Study for Effects of MLN9708 on Embryo-Fetal Development in Rats (non-GLP-compliant)*

Pregnant rats received either vehicle or ixazomib at doses of 0.1 and 0.3 mg/kg QD or 0.6 and 0.8 mg/kg Q3D (6 rats/group). As a result of severe maternal toxicity at 0.8 mg/kg Q3D (1 animal died and one was euthanized on day 7), surviving animals were reassigned to 0.4 mg/kg Q3D. After dosing was completed, dams were euthanized on GD 20. In rats dosed QD, decreases in body weight and food consumption were noted in dams in the 0.3 mg/kg group. Black-colored stools and a decrease in feces were observed transiently in 1 dam in the same group. No abnormal findings were observed in placentae or foetuses in any group. The NOAEL was determined to be 0.1 mg/kg (AUC24 = 184 hr*ng/mL) for dams and > 0.3 mg/kg for foetuses.

In rats dosed Q3D, at 0.6 mg/kg, decreases in body weight and food consumption was noted. Fetal weights were decreased and, although not statistically significant, there may have been a trend towards decreased fetal viability and increased post-implantation loss at 0.6 mg/kg. At necropsy on day 20 of gestation, no treatment-related findings were observed in any group (0.6 and 0.4 mg/kg). There were no statistically significant differences in the number of corpora lutea or implants and no treatment-related findings between the control group and treated group. The NOAEL was determined to be 0.4 mg/kg/3 days (AUC24 = 291 hr*ng/mL) for both dams and foetuses.

- *Study MLN9708-26378: Effects of MLN9708 on Embryo-Fetal Development in Rats*

A GLP-compliant study was conducted to evaluate the embryo-fetal developmental toxicity of ixazomib, as ixazomib citrate, administered PO to pregnant Sprague-Dawley rats on GD 6, 9, 12, and 15. Rats received either vehicle or ixazomib at doses of 0.2, 0.4, and 0.6 mg/kg (20 rats/group). After dosing was completed, main study dams were euthanized on GD 20.

Two dams administered 0.6 mg/kg were found dead on GD 7 and 8. Clinical signs in this group included soiled fur and decreased feces. Decreased maternal body weights with corresponding decreases in food consumption were noted at all dose levels. Examination at necropsy revealed small thymus in the 0.4- and 0.6-mg/kg groups, and a black discoloration on the stomach was observed in 1 animal at 0.6 mg/kg. No test article-related effects on the number of corpora lutea or implants were noted in any group, nor were there any test article-related effects in the macroscopic findings for the placentae. In the fetal examinations, the post-implantation loss rate, number of live fetuses, sex ratio, and fetal body weights were comparable among groups.

No test article-related effects were noted in the external observations in any group, or in the visceral/skeletal observations or number of sacro-caudal vertebrae in the 0.6-mg/kg group, relative to control.

From these results, the NOAEL was determined to be < 0.2 mg/kg/3 days (GD 15 AUC24 $= 201$ hr*ng/mL) for general toxicity of dams and ≥ 0.6 mg/kg/3 days for reproductive toxicity and embryo-fetal development.

- *Study WIL-416156: An Oral (Gavage) Dose Range-Finding Study of MLN9708 on Embryo/Fetal Development in Rabbits (GLP compliant)*

MLN9708 doses of 0 (vehicle control), 0.25, 0.5, 1.0, and 1.2 mg/kg were administered by oral gavage (6 females/each group) to pregnant New Zealand White [Hra:(NZW)SPF] rabbits approximately twice weekly on GD 7, 10, 13, 16, and 19. After dosing was completed, dams were euthanized on GD 29.

One dam in the 1.2 mg/kg group was found dead on GD 11. Two dams in the same group were euthanized in extremis (on GD 13 and GD 19) as a result of marked body weight losses and reduced food consumption. Clinical signs in these animals included decreased defecation, soft stool, diarrhea, mucoid feces, and brown material on the body surface.

At all doses, generally transient decreases in mean body weight and food consumption were noted in the dams, along with clinical signs of decreased defecation, diarrhea, and soft stool at doses ☐ 0.5 mg/kg. Surviving animals at 1.2 mg/kg also had lower gravid uterine weights than those observed in controls (14.1%).

Embryo-fetal effects were observed at 1.0 mg/kg and included post-implantation loss (early and late resorptions) and reduced fetal viability. There were no changes in intrauterine growth and no clear ixazomib-related fetal malformations or developmental variations at any dose.

The NOAEL for maternal toxicity was < 0.25 mg/kg (GD 19 $AUC_{72} <$549 hr*ng/mL) and for embryo-fetal effects was 0.5 mg/kg (GD 19 AUC72=956 hr*ng/mL).

- *Study 9708-28154: Effects of MLN9708 on Embryo-Fetal Development in Rabbits (GLP-compliant)*

Ixazomib citrate was administered on GD 7, 10, 13, 16, and 19 PO to pregnant New Zealand white rabbits. Rabbits received either vehicle or ixazomib at 0.1, 0.3, or 1.0 mg/kg (20 animals/group). After dosing was completed, dams were euthanized on GD 28.

There were no test article-related deaths, abortions, or premature delivery in any group.

At doses≥ 0.3 mg/kg, there were decreases in maternal body weight, body weight gain, and/or food consumption along with decreased feces. In the 1.0 mg/kg group, loose stool and soiled fur were also observed. There were no test article-related effects on the numbers of corpora lutea or implants, and on the placentae in any group. In the fetal examinations, no test article-related effects were noted in

the sex ratio, fetal weights, or visceral observations in any group. The frequency of abnormalities in caudal vertebrae was increased in the 1.0-mg/kg group, and 2 fetuses with caudal abnormalities showed short tail at external observation. In the skeletal variations, the frequency of the variation in the number of lumbar vertebrae and full supernumerary ribs was increased at doses≥ 0.3 mg/kg. However, the relationship between the pharmacological action and the skeletal features observed in this study was unclear.

The NOAEL of ixazomib was 0.1 mg/kg/3 days (GD 19 AUC24 = 189 hr*ng/mL) for maternal toxicity and embryo-fetal development and ≥ 1.0 mg/kg/3 days for reproductive function.

Toxicokinetic data

Comparative systemic exposure to ixazomib after oral administration to rats (7 cycles), dogs (10 cycles), and humans is presented in **Table 11**.

Table 11. Comparative Systemic Exposure to Ixazomib after Oral Administration to Rats (7 Cycles), Dogs (10 Cycles), and Humans

			Ixazomib Systemic (Plasma) Exposure[a]	
Species	Dose (mg/kg)	Dose Association	Mean C_{max} (ng/mL)	Mean AUC[b] (hr*ng/mL)
Rats[c]	0.2	NOAEL	5.99	483
Dogs[d]	0.10	NOAEL	136	1940
Human[e]	0.057[f]	N/A	37.0	1080

N/A = not applicable; NOAEL = no observed adverse effect level.
a Data are for both sexes combined. b Values represent AUC from the time 0 to 168 hours (AUC168) for rats, dogs, and humans. c Report WIL-416165. d Report WIL-416164. e Human exposure after oral (PO) doses of ixazomib administered once weekly (QW) for 3 weeks on a 28-day cycle; values represent Day 15 parameters. Data is pooled from Clinical Studies C16004, C16005, and C16007; n = 56 for Cmax; n = 42 for AUC168. f Based on a 4-mg dose and a 70-kg patient.

Summary of toxicokinetic parameters in pivotal repeat dose toxicology studies are presented in **Table 12**, **Table 13, Table 14, Table 15** and **Table 16**.

Table 12. Summary of Mean Plasma Toxicokinetics of Ixazomib after Twice-Weekly Oral Dosing of Ixazomib Citrate for 5 Cycles in Sprague-Dawley Rats

Dose[a] (mg/kg)	Day	t_{max} (hr)	C_{max} (ng/mL)	AUC_{24} (hr*ng/mL)
0.2	0	2.0	4.19	92.7
0.2	94	2.0	8.53	156
0.4	0	0.5	11.3	193
0.4	94	2.0	18.4	253
0.8	0	0.5	29.2	395
0.8/0.6[b]	94	0.5	26.1	296

Note: Days 0 and 94 represent Cycles 1 and 5, respectively.
a All doses are in terms of ixazomib. b The 0.8-mg/kg dose was reduced to 0.6 mg/kg before initiation of Cycle 3.

Table 13. Summary of Mean Plasma Toxicokinetics of Ixazomib after Once-Weekly Oral Dosing of Ixazomib Citrate for 7 Cycles to Sprague-Dawley Rats

Dose (mg/kg)	Day	t_{max} (hr)		C_{max} (ng/mL)		AUC_{168} (hr*ng/mL)	
		M	F	M	F	M	F
0.2	0	1.0	0.5	3.68	5.12	264	374
	14	1.0	1.0	7.04	7.83	641	569
	42	1.0	0.5	6.35	9.98	547	613
	168	0.5	4.0	5.42	6.55	489	476
0.4	0	1.0	1.0	8.97	13.0	655	742
	14	0.5	1.0	19.3	23.7	977	922
	42	0.5	0.25	12.0	18.7	879	884
	168	0.5	1.0	19.2	21.3	754	803
0.8/0.6[a]	0	1.0	0.5	21.4	66.4	1150	1660
	14	1.0	0.1	51.2	51.9	1420	1370
	42	0.5	0.25	30.5	69.7	1260	1300
	168	0.5	1.0	62.1	44.7	1200	1070

a Starting with Cycle 3 (Day 56), the dose level for the high-dose females was lowered from 0.8 to 0.6 mg/kg as a result of the overt toxicity and mortality (referred to hereafter as the 0.8/0.6-mg/kg group).

Table 14. Summary of Mean Plasma Toxicokinetics of Ixazomib after Twice Weekly Oral Dosing of Ixazomib for 1 Cycle in Beagle Dogs

Dose (mg/kg)	Day	C_{max} (ng/mL)		AUC_{24} (hr*ng/mL)	
		Males	Females	Males	Females
0.1	1	161	90.9	492	387
	11	159	NC[a]	678	NC
0.15	1	N/A	236	N/A	642
	11	N/A	NC	N/A	NC
0.2	1	220	293	753	1120
	11[b]	311	345	1460	1910
0.3	1	397	N/A	1590	N/A
	11[c]	NV	N/A	NV	N/A

N/A = not applicable; NC = not calculated; NV = no value.
Note: Days 1 and 11 represent Cycle 1. n = 5, unless otherwise specified.
a Not calculated because of the outlier toxicokinetic (TK) profile for this group of animals. b n = 4 for males; 1 male was euthanized in extremis on Day 9. c n = 3 for females; TK data from 2 animals were determined to be outliers and were excluded from mean TK parameter calculations.

Table 15. Summary of Mean Plasma Toxicokinetics of Ixazomib After Twice-Weekly Oral Dosing of Ixazomib Citrate for 5 Cycles in Beagle Dogs

Dose (mg/kg)	Day	t_{max} (hr)	C_{max} (ng/mL)	AUC_{24} (hr*ng/mL)
0.05	0	5.1	27.7	155
	94	4.4	43.5	388
0.10	0	1.9	53.2	307
	94	9.3	80.5	750
0.15	0	5.6	82.0	495
	94	5.0	137	1260

Note: Days 0 and 94 represent Cycles 1 and 5, respectively. n = 6 (0.05 mg/kg); n = 12 (0.10 and 0.15 mg/kg).

Table 16. Summary of Mean Plasma Toxicokinetics of Ixazomib After Once-Weekly Oral Dosing of Ixazomib Citrate for 10 Cycles in Beagle Dogs

Dose (mg/kg)	Day	t_{max} (hr)	C_{max} (ng/mL)	AUC_{24} (hr*ng/mL)	AUC_{168} (hr*ng/mL)
0.05	0	0.58	38.9	218	706
	14	0.71	36.2	206[a]	1070
	252	1.0	57.1	309	934
	266	0.75	83.5	410	NV[b]
0.10	0	0.58	107	609[c]	1900
	14	0.50	97.5	638[d]	2610
	252	0.71	136	695	1940
	266	0.50	162	828	NV[b]
0.20	0	0.48	277	1410	3300
	14	0.83	217	1390	3250
	252	0.44	333	1560	3900
	266	0.35	353	1870	NV[b]

Note: All doses are presented in terms of MLN2238 (administered as MLN9708). n =3/sex (0.05 mg/kg) and 6/sex (0.10 and 0.20 mg/kg) unless otherwise noted.
a n = 4. b Day 266 samples only collected to 24 hours post-dose per protocol. c n = 9. d n = 7.

Local Tolerance

Local tolerance of ixazomib was evaluated on the basis of the examination of injection sites or sites associated with oral gavage administration. Additionally, ixazomib citrate was tested in an *in vitro* human whole blood haemolysis assay to assess IV tolerance.

When evaluated in GLP-compliant PO toxicity studies up to 6 months (7 cycles) in rats and up to 9 months (10 cycles) in dogs, ixazomib (administered as ixazomib or as ixazomib citrate), at doses that were tolerated, had no local adverse effects on the upper GI tract.

When evaluated in repeat-dose IV GLP-compliant toxicity studies in rats and dogs, ixazomib (administered as ixazomib or as ixazomib citrate) had no local adverse effects at injection sites.

Additionally, ixazomib and ixazomib citrate did not induce haemolysis in i*n vitro* human whole blood assays.

Other toxicity studies

The purity of ixazomib citrate and ixazomib used in GLP-compliant studies was ≥ 99.0% and ≥ 98.24%, respectively. The impurity profile of the batches used for GLP-compliant studies was generally consistent with that of the batches used in pivotal clinical trials. In the GLP-compliant repeated-dose toxicology studies, total impurities in the drug substance or drug product of ixazomib citrate or ixazomib were ≤ 0.25% or 1.79%, respectively. Of note, 2 potential impurities were also identified as

metabolites M1 and M12 in rats and are therefore qualified as impurities in the drug substance. Additionally metabolite M3, another potential drug substance impurity, was detected as an *in vitro* metabolite in rats, dogs, and humans, but was not observed *in vivo* in animals because metabolite M3 was likely further metabolized into metabolite M12.

In a non-GLP-compliant phototoxicity study (MLN9708-24442) mouse embryonic BALB/3T3 cells were incubated with up to 400 ug/mL of ixazomib citrate for 1 hour and then irradiated for 50 minutes with ultraviolet A (UVA) light at a dose of 5 J/cm^2. Cells were washed and then incubated for 19 to 22 hours, and cell viability was determined. No precipitation of the drug was observed in cell medium at any concentration in either the nonirradiated or irradiated state. The concentration producing 50% inhibition (IC50) of cell viability for ixazomib was 30.579 ug/mL in the non-irradiated state and 19.806 ug/mL in the irradiated state. The photo-irritation-factor (PIF) was 1.54, which was not phototoxic (PIF < 2).

2.3.5. Ecotoxicity/environmental risk assessment

Table 17. Summary of main study results

Substance (INN/Invented Name): MLN2238, ixazomib, Ninlaro			
CAS-number (if available):			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow} (D_{ow})		log Kow 2.3	<4.5 threshold No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}		
	BCF		not B
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		not T
PBT-statement :	The test substance has not a PBT potential		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00011	µg/L	<0.01 ug/L threshold No
Other concerns (e.g. chemical class)			No

2.3.6. Discussion on non-clinical aspects

Ixazomib will be used in combination with lenalidomide and dexamethasone. There were no non-clinical studies to investigate the efficacy of this triple combination. No statement for the rationale for the proposed use of this combination could be found in the non-clinical dossier. Only the combination of ixazomib and lenalidomide were evaluated non-clinically. One study was conducted to evaluate the effects of combining ixazomib with lenalidomide using *in vitro* viability assays in MM cell lines. The combination of ixazomib with lenalidomide demonstrated synergistic effects on cell viability in the ANBL-6 and NCI-H929 cell lines, and additive effects in the RPMI-8226 and MM.1S cell lines. Notwithstanding the lack of non-clinical data, the efficacy of the triple combination is considered to be

based on the first interim analysis of clinical study C16010 (Clinical Efficacy section). The clinical data indicated that there is no need for additional non-clinical data.

Ixazomib demonstrated consequences of proteasome inhibition, as evidenced in cultured human embryonic kidney cell line (HEK 293) by stabilization of the 4xUb-Luc reporter, inhibition of the NF-κB-luciferase reporter, and accumulation of ubiquitinated proteins. The exploratory objectives reported in clinical study C16010 include the evaluation of the potential relationship between response or resistance to ixazomib treatment and proteasome and NF-kB-related genes, such as tumour necrosis factor receptor-associated factor-3 (TRAF-3), in blood samples. For median PFS, the HRs favoured the ixazomib regimen over the placebo regimen: in any case the statistically significance was reached, (HR=0.633; 95% CI: 0.411, 0.974; p=0.036). This data will be re-analyzed later in combination with gene expression. Moreover, data for TRAF-3 genotyping will be available. The Applicant was recommended to submit data analysis of TRAF-3 genotyping in patients enrolled in study C16010 after authorisation and at the same time to submit a re-analysis of preliminary data (however, the issues identified in the application prevent recommending to grant a marketing authorisation).

Non-clinical safety pharmacology studies both *in vitro* (on hERG channels) and *in vivo* (in telemetered dogs following single oral administration) demonstrated no effects of ixazomib on cardiovascular or respiratory functions at AUC more than 8-fold higher than the clinical value. Ixazomib has an acceptable safety pharmacology profile for the proposed indication.

Absorption was rapid after PO administration in both rats and dogs and slow after PO administration to rabbits. After a single PO dose of [14C] ixazomib citrate to Long-Evans rats, drug-derived radioactivity was widely distributed for up to 672 hours post-dose. After a single IV dose of [14C] ixazomib to Sprague-Dawley rats, drug-derived radioactivity was distributed widely up to 72 hours post-dose into most tissues, except those of the CNS. Also, exposure to total radioactivity in the dorsal root ganglion (DRG) was similar to that in the blood, and all drug-related material in blood was determined to be ixazomib. In mice, rats, dogs, monkeys, and humans, plasma protein binding of ixazomib was moderate to high. Ixazomib showed RBC partitioning in a concentration-dependent and saturable manner, which is most likely because of its binding to the proteasomes in RBCs.

All metabolites found in human liver microsome (HLM) studies were also found in rat and dog liver microsomal studies. In an *in vitro* study investigating CYP isoenzyme induction there was a decrease in CYP isozyme immune-reactive protein levels, the cause of which is unknown, however it may be the result of cytotoxicity.

The *in vitro* cell based studies showed that ixazomib is not a substrate of hepatic OATPs, and thus OATP inhibitors or genetic polymorphisms are unlikely to affect the disposition of ixazomib. Additionally, ixazomib is not an inhibitor of P-gp, BCRP, or MRP2 at concentrations up to 100 μM, and OCT2, OAT1, OAT3, OATP1B1, OAT1B3, MATE1, and MATE2-K at concentrations up to 10.0 μM.

A package of non-GLP- and GLP-compliant toxicology studies was conducted in several species (mice, rats, rabbits, and dogs). These studies included single and repeated dose PO and IV administration studies (with the duration of PO administration studies up to 6 months in rats and 9 months in dogs), genotoxicity studies, reproductive and developmental toxicology studies, and an *in vitro* phototoxicity study. The repeated-dose studies were conducted using a cyclical intermittent dosing schedule (21-day cycle) that was either more frequent than the clinical schedule, or in the case of the chronic studies, the same as the clinical schedule (28-day cycle).

It is noteworthy that a definitive cause of death in rats was not established for either single-dose or repeated-dose studies, but was attributed to GI tract and lymphoid toxicity.

In multi-cycle repeated-dose toxicity studies conducted in rats and dogs, the principal target organs included the gastrointestinal tract, lymphoid tissues, and the nervous system. In the 9 month study (10 cycles) in dogs orally administered with a dosing schedule mimicking the clinical regimen (28 day cycle), microscopic neuronal effects were generally minimal in nature and only observed at 0.2 mg/kg (4 mg/m2). The majority of target organ findings demonstrated partial to full recovery following discontinuation of treatment, with the exception of neuronal findings in the lumbar dorsal root ganglion and dorsal column.

Peripheral neuropathy involving sensory nerve axons has also been observed in monkeys, mice and dogs with bortezomib. In a clinical trial with ixazomib neuropathy was reported with an increased incidence in the treated group compared to the placebo group.

Ixazomib caused embryo-foetal toxicity in pregnant rats and rabbits only at maternally toxic doses and at exposures that were slightly higher than those observed in patients receiving the recommended dose. Studies of fertility and early embryonic development and pre- and post-natal toxicology were not conducted with ixazomib, but evaluation of reproductive tissues was conducted in the general toxicity studies. There were no effects due to ixazomib treatment on male or female reproductive organs in studies up to 6-months duration in rats and up to 9 months duration in dogs.

Ninlaro can cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity.

It is unknown whether ninlaro or its metabolites are excreted in human milk. No animal data are available. Ixazomib was not mutagenic in a bacterial reverse mutation assay (Ames assay) or clastogenic in a bone marrow micronucleus assay in mice. Ixazomib was positive in an in vitro clastogenicity test in human peripheral blood lymphocytes. However, ixazomib was negative in an in vivo comet assay in mice, in which percent tail DNA was assessed in the stomach and liver. Therefore, the weight of evidence indicates that ixazomib is not considered to present a genotoxic risk.

Following oral administration, a tissue distribution study in rats revealed that the brain and spinal cord were amongst the tissues with the lowest levels, suggesting that the penetration of ixazomib through the blood-brain barrier appears to be limited. However, the relevance to humans is unknown.

In a non-GLP-compliant phototoxicity study in BALB/3T3 clone A31 cells ixazomib did not elicit any phototoxic response.

The data indicated that ixazomib under the proposed therapeutic regimen, will not pose an immediate risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 18. Overview of clinical studies

Study No. No. of Sites Country	Study Status	Study Design/ Population	Measures of Efficacy	Dosing Regimen/ Dose/Route	Number of Subjects Planned/ Enrolled
Phase 3 Oral, Combination in Relapsed and/or Refractory Multiple Myeloma					
C16010 147 sites Global (26 countries)	Ongoing	Phase 3, randomized, double-blind, placebo-controlled Adult patients with RRMM	Primary: PFS Key secondary: OS in ITT population and OS in high-risk patients with del(17) Other secondary: • ORR (CR+PR); CR+VGPR • TTR, DOR • TTP • Pain response • OS and PFS in high-risk patients carrying del(17), t(4;14), or t(14;16)	Ixazomib (4 mg) or placebo: Days 1, 8, and 15 added to: Dexamethasone 40 mg PO Days 1, 8, 15, and 22 Lenalidomide 25 mg Days 1-21 of a 28-day cycle	Planned: 703 Enrolled: 722
Phase 1 Oral, Single Agent Weekly Dosing in Relapsed and/or Refractory Multiple Myeloma					
C16004 6 sites United States (US)	Closed	Phase 1 Adult patients with RRMM	ORR [primary endpoint: safety]; [secondary endpoints: PK and 20S proteasome inhibition]	Ixazomib PO once weekly (Days 1, 8, 15) 28-day cycles Dose-escalation 0.24 mg/m^2 to 3.95 mg/m^2 MTD determined to be 2.97 mg/m^2 (~equivalent to 5.5 mg fixed dosing)	Planned: 70 Enrolled: 60
Phase 1 Oral, Single Agent Twice Weekly Dosing in Relapsed and/or Refractory Multiple Myeloma					
C16003 5 sites US	Closed	Phase 1 Adult patients with RRMM	ORR [primary endpoint: safety]; [secondary endpoints: PK and 20S proteasome inhibition]	Ixazomib PO twice weekly (Days 1, 4, 8, 11) in 21-day cycles Dose-escalation 0.24 mg/m^2 to 2.23 mg/m^2 MTD determined to be 2 mg/m^2 (~equivalent to 3.7 mg fixed dosing)	Planned: 70 Enrolled: 60

2.4.2. Pharmacokinetics

Absorption

The absolute bioavailability of ixazomib was assessed using population PK analysis. The analysis was performed using PK data from 755 patients (108, IV administration; 647, oral administration) across 10 clinical studies. Ixazomib absorption is fast, with an overall median Tmax of approximately 1 hour post dose on both Days 1 and 15. After achieving Cmax, ixazomib exhibited a multi-exponential disposition profile.

After oral administration, peak plasma concentrations of ixazomib were achieved at approximately one hour after dosing. The mean absolute oral bioavailability is 58%. Ixazomib AUC increases in a dose proportional manner over a dose range of 0.2 to 10.6 mg.

In study C16009 patients received a single oral dose of 4 mg ixazomib either under fed or fasted conditions on Day 1 and again under the alternative food intake condition on Day 15. The fed conditions involved administration of ixazomib within 1 hour of starting consumption of a high-fat breakfast (consisting of 800-1000 calories in total, of which 50% are from fat). The median Tmax was 3 hours later under fed compared with fasted conditions and C_{max} and AUC_{0-216} were reduced by 69% and 28%, respectively, in the fed condition.

Distribution

Ixazomib is 99% bound to plasma proteins and distributes into red blood cells with a blood-to-plasma AUC ratio of 10. The steady-state volume of distribution is 543 L.

Elimination

Mean plasma clearance is 1.86 L/hr, blood clearance is lower therefore hepatic extraction is low. The plasma elimination half-life is 9.5 days. Blood elimination half-life appears longer (Study C16007).

In part A of Study C16016 (phase 1, 2-part, open-label study designed to characterize the mass balance, PK, metabolism, and excretion of oral ixazomib) 7 patients were enrolled and received a single oral solution of 4.1 mg [14C]-ixazomib containing approximately 500 nCi of TRA on Day 1. Blood was collected at predetermined time points for analyses of plasma PK of ixazomib over a 14-day period, urine PK and excretion of ixazomib over a 7-day period, plasma and whole blood TRA, and metabolite profiles over a 35-day period.

Complete urinary and faecal output was collected continuously during the initial confinement period (Days 1-8) for analysis of TRA and biotransformation products. On Days 14 and 21, patients were administered a single 4 mg ixazomib capsule. Patients were to return to the clinic in the evening before Days 14, 21, 28, and 35 for a 24-hour overnight clinic visit. To ensure defecation, two 15-mL oral doses of Milk of Magnesia were recommended to be administered 2 hours apart in the clinic in the evening on Day 7 and the evening of each overnight clinic visit (Days 13, 20, 27, and 34). One blood sample was collected at pre-dose on each of these site visit days. Urine and faecal samples were collected during the 24-hour overnight visits. Patients were instructed to collect faeces for a 24-hour period 1 day prior to returning to the clinic for their overnight visits.

After administration of a single oral dose of 14C-ixazomib to 5 patients with advanced cancer, 62% of the administered radioactivity was excreted in urine and 22% in the faeces. Unchanged ixazomib accounted for < 3.5% of the administered dose recovered in urine.

The combined TRA recovery from urine and faeces in Patient 58001-002 was 115% primarily due to a higher recovery (96.0%) in the urine compared to the other 4 patients in the PK-evaluable population.

Without data from Patient 58001-002, the mean (±SD) TRA recoveries of administered radioactivity from urine, faeces, and combined urine and faeces were 53.6±10.8%, 22.6±3.40%, and 76.2±13.0%, respectively, in 4 patients. On average (n=5), the total cumulative excretion of ixazomib-derived radioactivity in urine and feces was 59.0% by Day 14 after dosing. The excretion rate reached a plateau on Day 28 (mean total recovery of 79.4%) with less than 1% daily increment of changes thereafter.

In vitro biliary excretion of ixazomib was evaluated in sandwich-cultured human hepatocytes (SCHH), which were incubated with either 10 µM ixazomib or 5 µM [14C]-ixazomib. The mean biliary elimination index (BEI) for ixazomib was 0, whereas the mean BEI for total radioactivity was 7.2. Based on the plasma $AUC_{0\text{-}312h}$ ratio of ixazomib and ixazomib-related TRA, ixazomib accounted for the majority (% Mean±SD:70.0±14.2%) of the circulating component. Terminal half-life is not reported since limited PK sampling did not allow for its accurate determination.

Seven major metabolites of ixazomib were identified in hepatic microsomes derived from male CD-1 mice, Sprague-Dawley rats, beagle dogs, cynomolgus monkeys, and humans (pooled, male and female), and none were unique to humans. Oxidative deboronation of ixazomib to the hemiaminal metabolite (M1) was the major biotransformation pathway evident in all species. In human liver microsomal extracts, M1 was the major metabolite, followed by M3, while M2, M8, M12, M15, M19, and M20 were observed at lower levels. Human hepatocyte incubations showed M1 and M3 as the dominant metabolites, with M8 in smaller quantities.

The metabolism of ixazomib was preliminarily explored in 3 patients after oral administration of ixazomib 2 mg/m^2 twice weekly (Days 1, 4, 8, and 11 of a 21-day cycle) in Study C16003. Plasma samples obtained after dosing on Days 1 and 11 were pooled and analysed for preliminary metabolite identification. Unchanged ixazomib was the major drug-related component observed on both days in human plasma. Only 1 metabolite (M8) was present in appreciable levels (~10% of parent by comparison of AUC0-8h). Other metabolites previously identified in human liver microsomes or human hepatocytes were not detected in human plasma.

The contribution of 7 CYP isozymes to ixazomib metabolism was evaluated using human complementary deoxyribonucleic acid (cDNA) CYP-expressing recombinant microsomes (rCYPs). The percentage contribution of individual CYP isozymes to the liver microsomal metabolism of ixazomib was then calculated using abundance factors for these CYP isozymes. At the 10 µM substrate concentration, CYP3A4 was the major CYP isozyme contributing to the metabolism of ixazomib, followed by CYP1A2. The relative contributions of the 7 major CYP isozymes were: 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), CYP2C19 (4.8%) and 2C9 (<1%). Note that this study was conducted at supra-therapeutic concentrations (10 µM ixazomib) that are >90-fold higher than the geometric mean clinical Cmax (0.11 µM) at the 4 mg oral once-weekly dose.

At 0.1 and 0.5 µM substrate concentrations, which are closer to clinical circulating concentrations of ixazomib following oral administration at a dose of 4 mg (geometric mean Cmax of 0.11 µM), there was little difference between the rates of metabolism of ixazomib in rCYP isozymes and in the presence of only control protein.

Dose proportionality and time dependencies

Dose proportionality

In Study C16004, ixazomib was administered orally once weekly for 3 weeks (Days 1, 8, and 15) in 28-day cycles. Patients with RRMM were enrolled into the following dosing cohorts: 0.24, 0.48, 0.80, 1.20, 1.68, 2.23, 2.97, and 3.95 mg/m^2. Blood samples were collected at multiple time points after

dosing on Days 1 and 15 to characterize the plasma PK profile of ixazomib. The Day 1 and Day 15 plasma PK parameters are summarised in **Table 19**.

Table 19. Plasma Pharmacokinetic Parameters of Ixazomib Following Once Weekly Oral Administration of Ixazomib in Patients with RRMM (Study C16004, Escalation and Expansion Cohorts)

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

Parameters are presented as geometric mean (%CV), except for Tmax which is presented as median (range). Individual values are reported if N<3. a N=17 for AUC0-168 and DN AUC0-168. b N=11 for t1/2, 10 for AUC0-168, and DN AUC0-168 and 8 for the accumulation ratio.

Definitive assessment of dose-proportionality/PK linearity was based on the cross-study population PK analysis. Ixazomib shows dose-linear PK, based on the population PK analysis with no readily apparent relationship between dose (0.2-10.6 mg) and clearance.

Time dependencies

Table 20. Pharmacokinetic Parameters of Ixazomib in Plasma and Whole Blood Following Once Weekly Oral Administration of Ixazomib in Patients with AL Amyloidosis (Study C16007)

	Ixazomib Dose			
	4 mg		5.5 mg	
Parameters (Units)	**Plasma**	**Whole Blood**	**Plasma**	**Whole Blood**
Day 1				
N	15[a]	16[b]	-	-
T_{max} (hr)	1 (0.5-2)	1.03 (0.5-6)	-	-
C_{max} (ng/mL)	41.6 (80)	98.9 (40)	-	-
AUC_{0-168} (ng•hr/mL)	577 (142)	7340 (41)	-	-
DN C_{max} (ng/mL/mg)	10.4 (80)	24.7 (40)	-	-
DN AUC_{0-168} (ng•hr/mL/mg)	144 (142)	1840 (41)	-	-
C_{max} blood-to-plasma ratio[c]	-	2.38 (56)	-	-
AUC_{0-168} blood-to-plasma ratio[d]	-	12.7 (64)	-	-
Day 15				
N	18[e]	17[f]	2	2
T_{max} (hr)	1 (0.5-6.08)	1.03 (0.5-6.02)	0.5, 1	0.5, 1
C_{max} (ng/mL)	40.7 (66)	125 (17)	61.4, 123	176, 203
AUC_{0-168} (ng•hr/mL)	990 (42)	9780 (20)	1240, 2210	13700, 15200
DN C_{max} (ng/mL/mg)	10.2 (66)	31.3 (17)	11.2, 22.4	32, 36.9
DN AUC_{0-168} (ng•hr/mL/mg)	248 (42)	2440 (20)	225, 402	2490, 2760
C_{max} blood-to-plasma ratio	-	2.89 (65)	-	1.65, 2.87
AUC_{0-168} blood-to-plasma ratio	-	9.86 (50)	-	6.20, 12.3
Accumulation Ratio for AUC_{0-168}	2.09 (18)	1.45 (9)	-	-

Parameters are presented as geometric mean (%CV), except for Tmax which is presented as median (range). Individual values are reported if N<3.
a N=14 for AUC0-168 and DN AUC0-168. One patient had a Cmax of 163 ng/mL and an AUC0-168 of 5010

ng•hr/mL, which were approximately 5 and 9-fold higher (respectively) than the median values. When this patient was excluded from the analysis, Cmax was 37.7 (69) ng/mL, AUC0-168 was 489 (49) ng•hr/mL, DN Cmax was 9.43 (69) ng/mL/mg, and DN AUC0-168 was 122 (49) ng•hr/mL/mg. b One patient had a Cmax of 230 ng/mL and an AUC0-168 of 18200 ng•hr/mL, which were approximately 2.5-fold higher than the median values. When this patient was excluded from the analysis, Cmax was 93.5 (26) ng/mL, AUC0-168 was 6910 (22) ng•hr/mL, DN Cmax was 23.4 (26) ng/mL/mg, DN AUC0-168 was 1730 (22) ng•hr/mL/mg, Cmax blood-to-plasma ratio was 2.47 (54), and AUC0-168 blood to-plasma ratio was 14.0 (59). c N=15. d N=14. e N=15 for AUC0-168, DN AUC0-168, and 10 for the accumulation ratio. f N=14 for AUC0-168, DN AUC0-168, and AUC0-168 blood-to-plasma ratio and 11 for the accumulation ratio.

The geometric mean terminal half-life for ixazomib is 9.5 days based on the population PK analysis.

For both IV and oral dosing, there is an approximately average 3-fold accumulation (based on AUC ratio) following the Day 11 dose for the twice-weekly schedule (C16001, C16003, C16008) and a 2-fold accumulation (based on AUC ratio) following the Day 15 dose for the once-weekly schedule (C16002, C16004, C16007, C16005).

Trough concentrations increase throughout Cycle 1, indicating that the steady state is not achieved with the twice-weekly or once-weekly dosing regimens by the time of administration of the last dose in a cycle.

Special populations

Impaired renal function

Patients with mild or moderate renal impairment (CrCL ≥30 mL/min) have been included in all clinical studies during the development of ixazomib. CrCL (≥30 mL/min) was not identified as a significant covariate in the population PK model. The magnitudes of percent difference in AUC at the 5th or 95th percentiles of CrCL relative to the median AUC was <20% suggesting lack of a clinically meaningful impact of CrCL (≥30 mL/min) on ixazomib PK.

A dedicated study (Study C16015) in patients with renal impairment was also performed in patients with severe renal impairment and in ESRD patients requiring hemodialysis. In Study C16015, a single dose of ixazomib (3 mg) was administered orally in the PK cycle to patients with normal renal function (Arm 1; CrCL ≥90 mL/min) and to patients with severe renal impairment (Arm 2; CrCL <30 mL/min, including patients with ESRD, which was defined as renal failure requiring hemodialysis). CrCL for entry into the study was calculated using the Cockcroft-Gault formula. ESRD patients requiring hemodialysis were enrolled such that the first hemodialysis treatment was approximately 24 to 28 hours postdose. Blood samples were collected at multiple time points after dosing (up to 336 hours) to characterize the plasma PK of ixazomib. The results are presented in Table 21.

Table 21. Plasma Pharmacokinetic Parameters of Ixazomib Following Single Dose Oral Administration of Ixazomib in Patients with Normal Renal Function or Severe Renal Impairment or Patients with ESRD Requiring Dialysis (Study C16015)

	Renal Function Category		
Parameter	**Normal Function**	**Severe Impairment**	**ESRD**
Total PK Parameters			
N	18[a]	14[b]	6
T_{max} (hr)[c]	1.04 (0.467-4)	1 (0.45-1.5)	1.25 (0.983-7)
C_{max} (ng/mL)	25.8 (56)	45.3 (81)	18.7 (82)
AUC_{0-168} (hr•ng/mL)	347 (42)	578 (51)	537 (30)
AUC_{0-last} (hr•ng/mL)	575 (38)	813 (51)	783 (35)
DN C_{max} (ng/mL/mg)	8.60 (56)	15.1 (80)	6.23 (82)
DN AUC_{0-168} (hr•ng/mL/mg)	116 (42)	193 (51)	179 (30)
DN AUC_{0-last} (hr•ng/mL/mg)	192 (38)	271 (51)	261 (35)
Unbound PK Parameters			
C_{max} (ng/mL)	0.30 (66)	0.478 (86)	0.213 (57)
AUC_{0-168} (hr•ng/mL)	4.03 (62)	6.11 (58)	6.12 (50)
AUC_{0-last} (hr•ng/mL)	6.64 (61)	9.25 (55)	8.93 (55)
DN C_{max} (ng/mL/mg)	0.10 (66)	0.159 (86)	0.071 (57)
DN AUC_{0-168} (hr•ng/mL/mg)	1.34 (62)	2.04 (58)	2.04 (50)
DN AUC_{0-last} (hr•ng/mL/mg)	2.21 (61)	3.08 (55)	2.97 (55)

Abbreviations: AUC0-168=area under the plasma ixazomib concentration-time curve from time 0 to 168 hours postdose; AUC0-last=area under the plasma ixazomib concentration-time curve from time 0 to the time of the last quantifiable concentration (only calculated for patients with samples collected through Day 15 of Part A); Cmax=maximum observed plasma concentration; DN=dose-normalized; ESRD=end-stage renal disease; N=number
of patients; Tmax=first time of Cmax.
a N=15 for AUC0-last, dose-normalized AUC0-last, unbound AUC0-last, and unbound dose-normalized AUC0-last.
b N=10 for AUC0-last, dose-normalized AUC0-last, unbound AUC0-last, and unbound dose-normalized AUC0-last.
c Median and range.

In the clinical study C16015, the AUC is 39% and 34% higher respectively in patients with severe renal impaired patients and those with ESRD than in those with normal function.

Geometric Least Squares Mean Ratios (90% Confidence Intervals) for Unbound C_{max} and $AUC_{0\text{-last}}$

Parameter	Geometric Least Squares Mean Ratio (90% CI)		
	Severe RI vs Normal Function	ESRD vs Normal Function	Combined (Severe RI/ESRD) vs Normal Function
Unbound C_{max} (ng/mL)	1.60 (0.99-2.58)	0.71 (0.38-1.34)	1.25 (0.79-1.98)
Unbound $AUC_{0\text{-last}}$ (hr•ng/mL)	1.39 (0.88-2.20)	1.34 (0.78-2.31)	1.38 (0.93-2.04)

Source: Table 14.2.1.4A and Table 14.2.1.4B

Abbreviations: $AUC_{0\text{-last}}$ = area under the plasma ixazomib concentration-time curve from time 0 to the time of the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; ESRD = end-stage renal disease requiring dialysis; RI = renal impairment.

Accordingly, a reduced starting dose of ixazomib (3 mg) is recommended in these groups of patients.

Impaired hepatic function

Patients with mild hepatic impairment (total bilirubin>1-1.5 times the upper limit of normal [ULN]) have been included in all clinical studies during the development of ixazomib, including Study C16010. Bilirubin was not identified as a significant covariate on clearance in the population PK model, and differences in the individual predicted exposures suggested no clinically meaningful impact of total bilirubin (>1-1.5xULN) on ixazomib PK.

A dedicated study in patients with hepatic impairment was also performed. Study C16018 was a phase 1 pharmacokinetic study of oral ixazomib in patients with advanced solid tumours or hematologic malignancies with varying degrees of liver dysfunction (as defined by the National Cancer Institute Organ Dysfunction Working Group). Out of 48 patients enrolled in the study a total of 43 patients were PK evaluable (12 with normal hepatic function, 13 with moderate hepatic impairment, and 18 with severe hepatic impairment). Patients were assigned to 1 of 3 hepatic function groups on the basis of their total bilirubin and aspartate aminotransferase (AST) values. The dose of ixazomib was dependent on hepatic function. Patients with normal function, moderate or severe impairment received 4 mg, 2.3 mg and 1.5 mg ixazomib, respectively. The results are presented in **Table 22**.

Table 22. Plasma Pharmacokinetic Parameters of Ixazomib Following Single Dose Oral Administration of Ixazomib in Patients with Normal Hepatic Function or Moderate or Severe Hepatic Impairment (Study C16018)

	Hepatic Function Category		
Parameter	Normal Function 4 mg	Moderate Impairment 2.3 mg	Severe Impairment 1.5 mg
Total PK Parameters			
N	12	13[a]	18[b]
T_{max} (hr)[c]	0.95 (0.48-4)	1.5 (0.5-2.5)	1.21 (0.5-4)
C_{max} (ng/mL)	61.0 (54)	42.5 (63)	26.1 (70)
AUC_{0-168} (hr•ng/mL)	836 (44)	576 (44)	464 (54)
AUC_{0-last} (hr•ng/mL)	1160 (41)	846 (49)	489 (50)
DN C_{max} (ng/mL/mg)	**15.3 (54)**	**18.5 (63)**	**17.4 (70)**
DN AUC_{0-168} (hr•ng/mL/mg)	**209 (44)**	**250 (44)**	**310 (54)**
DN AUC_{0-last} (hr•ng/mL/mg)	**289 (41)**	**368 (49)**	**326 (49)**
Unbound PK Parameters			
C_{max} (ng/mL)	0.509 (47)	0.372 (80)	0.232 (84)
AUC_{0-168} (hr•ng/mL)	6.98 (49)	5.16 (57)	4.14 (63)
AUC_{0-last} (hr•ng/mL)	9.65 (50)	7.33 (61)	4.44 (63)
DN C_{max} (ng/mL/mg)	**0.127 (47)**	**0.162 (80)**	**0.154 (84)**
DN AUC_{0-168} (hr•ng/mL/mg)	**1.75 (49)**	**2.24 (57)**	**2.76 (63)**
DN AUC_{0-last} (hr•ng/mL/mg)	**2.41 (50)**	**3.19 (61)**	**2.96 (63)**

Abbreviations: AUC0-168=area under the plasma ixazomib concentration-time curve from time 0 to 168 hours postdose; AUC0-last=area under the plasma ixazomib concentration-time curve from time 0 to the time of the last quantifiable concentration (only calculated for patients with samples collected through Day 15 of Part A); Cmax=maximum observed plasma concentration; DN=dose-normalized; N=number of patients; Tmax=first time of Cmax.
a N=12 for AUC0-168, dose-normalized AUC0-168, unbound AUC0-168, unbound dose-normalized AUC0-168 and 10 for AUC0-last, dose-normalized AUC0-last, unbound AUC0-last, and unbound dose-normalized AUC0-last. b N=14 for AUC0-168, dose-normalized AUC0-168, unbound AUC0-168, unbound dose-normalized AUC0-168 and 11 for AUC0-last, dose-normalized AUC0-last, unbound AUC0-last, and unbound dose-normalized AUC0-last. c Median and range

Unbound dose-normalized AUC0-last was increased by 27% in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function.

Geometric Least Squares Mean Ratios (90% Confidence Intervals) for Unbound Dose-Normalized C_{max} and AUC_{0-last}

	Geometric Least Squares Mean Ratio (90% CI)		
Parameter	Moderate Impairment vs Normal Function	Severe Impairment vs Normal Function	Combined (Moderate/Severe Impairment) vs Normal Function
Unbound DN C_{max} (ng/mL/mg)	1.27 (0.74-2.18)	1.21 (0.74-2.01)	1.24 (0.79-1.95)
Unbound DN AUC_{0-last} (hr·ng/mL/mg)	1.32 (0.70-2.50)	1.23 (0.66-2.29)	1.27 (0.75-2.16)

Source: Table 14.2.1.3A and Table 14.2.1.3B
Abbreviations: AUC_{0-last} = area under the plasma ixazomib concentration-time curve from time 0 to the time of the last quantifiable concentration; CI=confidence interval; C_{max}=maximum observed plasma concentration; DN = dose-normalized.

Therefore, a reduced starting dose (3 mg) of ixazomib is recommended for patients with moderate or severe hepatic impairment.

Gender

The effect of sex as a covariate on AUC was evaluated in Population PK analysis and was found to be no significant.

Race

Two studies were conducted in Asian populations: C16013 (Asian) and TB-MC010034 (Japanese).

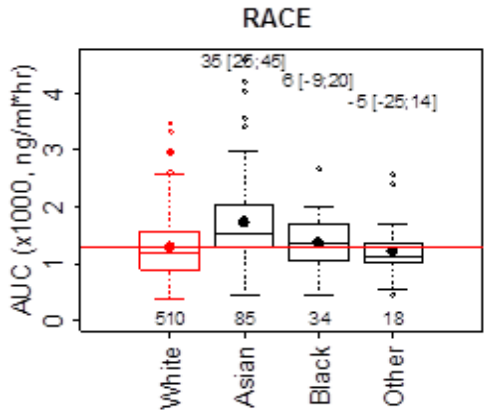
In Study C16013, ixazomib (4 mg) was administered orally once weekly for 3 weeks (Days 1, 8, and 15) in 28-day cycles. Patients also received lenalidomide (25 mg) on Days 1 through 21, and dexamethasone (40 mg) on Days 1, 8, 15 and 22, in 28-day cycles. Blood samples were collected at multiple time points after ixazomib administration on Days 1 and 15 of Cycle 1 to characterize the PK of ixazomib, in combination with Lenalinomide and Dexamethasone, in adult Asian patients with RRMM. A total of 24 patients (10 Chinese, 10 Korean and 4 ''Other'') enrolled in Singapore, Hong Kong and South Korea were included in the PK-evaluable population.

Ixazomib was rapidly absorbed after oral administration on both Days 1 and 15 with the overall median Tmax in Asian patients of 1.5 hours and 2 hours, respectively. Ixazomib plasma concentrations declined in a multiexponential manner with a slow terminal phase. The overall geometric mean t1/2 after multiple dosing was 144 hours (6 days) and the geometric mean accumulation ratio for AUC0-168 on Day 15 was 2.46. AUC0-168 values in the 3 Asian subgroups were similar after both single and multiple dosing. Additionally, a <25% difference in the Day 15 geometric mean AUC0-168 was noted across the Asian subgroups/races.

In study TB-MC010034 mean plasma concentrations of ixazomib in ixazomib monotherapy were higher than those observed in the combination therapy cohort on Day 1: however, similar profiles for ixazomib were observed in ixazomib monotherapy and combination therapy on Day 15. Ixazomib was rapidly absorbed after single and multiple oral dose administration, both as monotherapy and combination therapy, with a median Tmax of 1-2 hours. After Tmax, ixazomib concentrations declined in a multiexponential manner with a slow terminal phase (geometric mean t1/2 of 125 hours in the combination therapy cohort to 137 hours in the monotherapy cohort). The accumulation ratios for AUC0-168 after monotherapy and combination therapy were approximately 2.1 and 1.8, respectively.

The effect of race on the PK of ixazomib was investigated using population PK analysis (**Figure 4**).

Figure 4. Boxplots for Individual Predicted Exposure Stratified by Race for Patients Receiving Oral 4 mg Ixazomib



Red and black dots indicate the mean exposure in the most prevalent category and in other categories, respectively.
Numbers (brackets) in the top of plots show the percent change in AUC∞ (with 95%CI) in other categories relative to the most prevalent category, while numbers at the bottom show patients in each category.

Weight

There was no effect of body surface area (1.2 to 2.7 m^2), on the clearance of ixazomib based on the results of a population PK analysis.

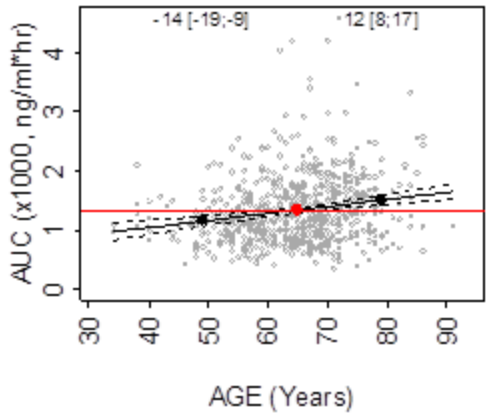
Age

Table 23. Patients Included in the Population Pharmacokinetic Analysis of Ixazomib by Age Category

Parameter	Age in years		
	65-74 (Older subjects number/ total number, [%])	75-84 (Older subjects number/ total number, [%])	≥85 (Older subjects number/ total number, [%])
Pharmacokinetic trials[a]	285/755 (38)	86/755 (11)	7/755 (<1)
a The patient breakdown by age category is presented out of the 755 total patients included in the population pharmacokinetic analysis.			

In the population PK analysis, the age range examined was 23-91 years (**Figure** 5).

Figure 5. Correlation between age and individual predicted exposure in patients receiving oral 4 mg ixazomib



Red and black dots indicate the median and 5th and 95th percentile of individual covariate values. Numbers (brackets) show the percent change in AUC0-∞ at the 5th and 95th percentile relative to the value at the median, based on the shown linear regression (and 95%CI).

The PK of ixazomib has not been characterized in paediatric patient populations.

Pharmacokinetic interaction studies

- ***In vitro***

Metabolism appears to be the major route of elimination for ixazomib. *In vitro* studies indicated that ixazomib is metabolized by multiple CYP450 and non-CYP enzymes/proteins. The effect of strong CYP1A2 inhibitors on the PK of ixazomib was examined in the population PK analysis. These CYPs were chosen for investigation based on the rank order of relative biotransformation activity for 10 µM ixazomib of the major human CYP isozymes where they contributed >25% to the metabolism of ixazomib in rCYPs.

Ixazomib is neither a time-dependent nor reversible inhibitor of CYPs 1A2, 2B6, CYP2C8, 2C9,

2C19, 2D6, or 3A4 (IC50 >30 μM, Ki >15 μM), therefore the potential for ixazomib to produce

DDIs via CYP isozyme inhibition is low. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4 activity or corresponding immunoreactive protein levels under conditions where prototypical inducers caused anticipated increases in CYP activity (with ixazomib concentrations up to 9.67 μM). Therefore, ixazomib is unlikely to produce DDIs via induction of metabolism- or transporter-mediated clearance of co-administered drugs, as it did not induce expression of any of the representative sensitive downstream CYP enzymes that are induced via AhR (eg, CYP1A2), CAR (eg, CYP2B6) or PXR (eg, CYP3A4/5).

Ixazomib is not a substrate of OATP transporters in human hepatocytes based on comparison of ixazomib uptake rates in the presence and absence of known OATP inhibitors (rifampin and cyclosporine A). On the basis of these *in vitro* findings, there is low probability of ixazomib disposition being affected by OATP1B1 or OATP1B3 inhibitors or inducers, or by clinically meaningful genetic polymorphisms in OATP1B1 or OATP1B3.

Ixazomib was not evaluated *in vitro* as a potential substrate of OAT1, OAT3, or OCT2. However, these renal uptake transporters are unlikely to be major determinants of ixazomib clearance, as the renal clearance of unchanged ixazomib (0.119 L/hr, Study C16016) is approximately 3.7% of ixazomib CL/F and 6.4% of CL. In addition, the renal clearance of unchanged ixazomib (0.119 L/hr) is similar to the product of the fraction unbound and glomerular filtration rate (GFR) (fu*GFR=0.072 L/hr), suggesting that glomerular filtration instead of active secretion is the predominant mechanism of renal clearance. As such, the risk of DDIs between ixazomib and inhibitors or inducers of OAT1, OAT3, and OCT2 is predicted to be low.

Ixazomib was shown *in vitro* to be a low affinity substrate of the efflux transporter P-gp but not BCRP or MRP2. The membrane permeation clearance (Vmax/Km) of ixazomib by passive diffusion and efflux transporters was 10.6 and 2.4 μL/hr, respectively. P-gp-mediated transport accounted for 19% of the total transport of ixazomib in Caco-2 cells, indicating the contribution of P-gp to the overall membrane permeation clearance of ixazomib is low. Considering the low contribution of P-gp to the permeability clearance of ixazomib in Caco-2 cells, and the physicochemical properties of ixazomib (moderate permeability and high solubility), it is unlikely that P-gp-mediated efflux in the intestine is a major determinant of the absolute oral bioavailability of ixazomib. Consistently, ixazomib showed dose-linear PK following oral dosing over the 0.2 to 10.6 mg dose range (from population PK analysis). In addition, biliary secretion and renal secretion of unchanged ixazomib are estimated to be minor routes of elimination relative to hepatic metabolism. A low extent of biliary elimination of ixazomib (<10% BEI) was observed in human hepatocytes. Furthermore, renal clearance of unchanged ixazomib accounts for approximately 3.7% of ixazomib CL/F and 6.4% of CL, and as noted earlier, is consistent with passive glomerular filtration as opposed to active tubular secretion.

Studies in Caco-2 cells showed that ixazomib is not an inhibitor of P-gp or BCRP (IC50 >100 μM) and studies in the MRP2-transfected membrane vesicle model, showed ixazomib is not an inhibitor of MRP2 at concentrations of 0.02 to 100 μM. Consequently, ixazomib is not anticipated to inhibit P-gp, BCRP, or MRP2 at total maximum plasma concentrations or at estimated intestinal lumen concentrations associated with a 4 mg oral dose of ixazomib administered once weekly on Days 1, 8, and 15 of a 28-day cycle. Given the low risk of DDIs between ixazomib and P-gp, BCRP, or MRP2 substrates, in vivo DDI studies were not conducted with probe substrates of these efflux transporters.

Ixazomib is not an inhibitor of hepatic OATPs (IC50 >10 μM). Ixazomib is therefore not expected to inhibit hepatic OATPs at total maximum plasma concentrations or at estimated unbound maximum hepatic inlet concentrations associated with a 4 mg oral dose administered once weekly on Days 1, 8,

and 15 of a 28-day cycle. Therefore, the risk of ixazomib interacting with OATP substrates is predicted to be low. As such, *in vivo* DDI studies were not conducted with ixazomib and a known substrate of OATP.

Studies in human hepatocytes or transporter expressing cell lines showed that ixazomib is not an inhibitor of OATP1B1, OATP1B3, OCT 2, OAT1, OAT3, MATE 1 and MATE2-K at clinically relevant concentrations (IC50 >10 μM). Ixazomib is therefore not anticipated to inhibit OCT2, OAT1, or OAT3 at unbound maximum plasma concentrations associated with a 4 mg oral dose of ixazomib administered once weekly on Days 1, 8, and 15 of a 28-day cycle. Ixazomib is also not expected to inhibit MATE1 or MATE2-K at clinically relevant concentrations. Thus, there is low potential for ixazomib to cause DDIs with OCT2, OAT1, OAT3, MATE1, or MATE2-K substrates.

- ***In vivo***

In vivo drug-drug interaction in patients was evaluated in Study C16009. Study C16009 was a 5-arm phase 1 study and three of the arms were designed to assess the potential DDIs with strong CYP3A inhibitors (Arms 1 and 5) and CYP3A inducers (Arm 4).

Arm 1 evaluated the effect of the strong CYP3A inhibitor, ketoconazole, on the PK. Sixteen PK-evaluable patients received a single, 2.5 mg, oral dose of ixazomib on Day 1 in the absence of ketoconazole (Period 1) and on Day 15 of Cycle 1 in the presence of ketoconazole (Period 2). Oral ketoconazole (400 mg) was administered once daily on Days 12 through 25 of Cycle 1. Ixazomib Cmax was similar when ixazomib was co-administered with or without ketoconazole with a corresponding LS geometric mean ratio (90% CI) of 1.01 (0.78-1.30) whereas the AUC0-264 was higher (approximately doubled) in the presence of ketoconazole with a corresponding LS geometric mean ratio (90% CI) of 2.08 (1.91-2.27).

This arm (arm 1) of the study used a fixed-sequence design. A period effect on plasma exposures was observed during the statistical analysis of PK data from Arms 2 and 3 of this study that employed a 2-way crossover design. The ANOVA analysis for AUC0-216, indicated higher exposures in Period 2 versus Period 1 (ratio of Period 2 AUC to Period 1 AUC estimated as 1.63, [calculated from the estimate of 0.4858 on log-transformed data]).

For this reason the true treatment effect of a strong inhibitor of CYP3A on the PK of ixazomib estimated in Arm 1 may have been confounded (ie, overestimated) by a potential period effect. As a result, Arm 5 was added to the study with Amendment 4 to characterize the single-dose PK of ixazomib when co-administered with the strong CYP3A inhibitor, clarithromycin.

In Arm 5, after 5 days of clarithromycin (500 mg twice daily) pre-treatment, 15 PK-evaluable patients received a single 2.5 mg oral dose of ixazomib on Day 6 of Cycle 1. Twice daily administration of clarithromycin continued on Days 6 to 16 of Cycle 1. Ixazomib Cmax and AUC0-264 were similar when ixazomib was co-administered with (Arm 5) or without (Arm 1) clarithromycin with corresponding LS geometric mean ratios (90% CI) of 0.96 (0.67-1.36) and 1.11 (0.86-1.43), respectively.

Arm 4 evaluated the effect of the strong CYP3A inducer, rifampin, on the PK of ixazomib. After 7 days of rifampin (600 mg once daily) pre-treatment, 16 PK-evaluable patients received a single 4 mg oral dose of ixazomib on Day 8 of Cycle 1. Administration of rifampin continued on Days 8 to 14 of Cycle 1. Rifampin co-administration resulted in lower plasma concentrations of ixazomib throughout the 168 hours post-dose interval. Ixazomib Cmax was reduced in the presence of rifampin by approximately 54%; corresponding LS geometric mean ratio (90% CI) of 0.46 (0.29-0.73). Ixazomib AUC0-last was reduced by approximately 74%; corresponding LS geometric mean ratio (90% CI) of 0.26 (0.18-0.37). Median Tmax was similar (approximately 1.5 hours) with and without rifampin co-administration.

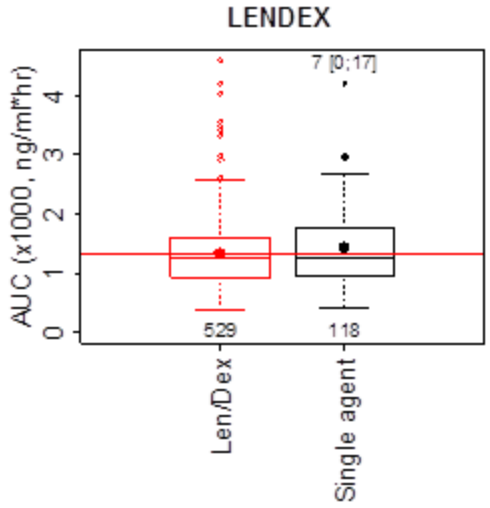
The effect of strong CYP1A2 inhibitors (eg, ciprofloxacin) on the PK of ixazomib was examined in the population PK analysis as a time-dependent categorical covariate. The analysis dataset included 36 patients on ciprofloxacin (strong CYP1A2 inhibitor) during the active ixazomib treatment period. The population PK analysis indicated a 9% higher ixazomib AUC (95% CI of 6-12%) for patients receiving strong CYP1A2 inhibitors compared to those not receiving strong CYP1A2 inhibitors; thereby, suggesting that no dose adjustment is necessary for ixazomib when coadministered with strong inhibitors of this drug metabolizing enzyme.

CYP1A2 activity is induced by smoking. Smoking status was not identified as a significant covariate in the population PK analysis, which suggests that CYP1A2 inducers do not significantly alter the PK of ixazomib. In addition, the individual predicted exposures following a single 4 mg ixazomib dose were calculated using the final model. The magnitude of percent difference in AUC between patients who self-identified themselves as current smokers and patients who have never smoked was <20% suggesting no clinically meaningful difference in exposures between the two groups . However, it is important to note that the smoking history was self-reported.

Effect of Lenalidomide/Dexamethasone on PK of Ixazomib

PK parameters for ixazomib coadministered with LenDex (Studies C16005 and C16008), are similar to those observed when ixazomib is administered as a single agent (Studies C16004 and C16003).

Figure 6. Individual Predicted Exposure Stratified by LenDex Combination and Single Agent Treatment for Patients Receiving Oral Ixazomib



Red and black dots indicate the mean exposure in the most prevalent category and in other categories. Numbers (brackets) in the top of plots show the percent change in AUC0-∞ (with 95%CI) in other categories relative to the most prevalent category, while numbers at the bottom show patients in each category.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical pharmacodynamic studies were submitted.

Primary and Secondary pharmacology

The pharmacodynamic effect of ixazomib was assessed by measuring the inhibition of 20S proteasome activity in whole blood after once-weekly and twice-weekly IV bolus dosing of ixazomib in Studies C16001 and C16002. Maximum inhibition (Emax) of 20S proteasome activity occurred within 30

minutes in most patients, indicating rapid target engagement in blood. Maximum 20S proteasome inhibition was dose-dependent. Mean Emax values ranged from <10% in the 0.125 mg/m^2 twice-weekly dosing cohort to approximately 70% in the 2.34 mg/m^2 twice-weekly dosing cohort in Study C16001. Similar results were observed following once-weekly dosing with approximately 80% inhibition at doses of at least 2.34 mg/m^2. Prolonged inhibition of 20S proteasome activity (>24 hours) was not apparent in either study.

Effect on QT interval

PK-matched triplicate ECG measurements were collected in 4 phase 1 studies (IV studies C16001 and C16002, and oral studies C16003 and C16004) to develop a model relating QTc intervals to plasma concentrations of ixazomib. A linear mixed effects models with fixed effects (study, sex, study day, time), and random effects (intercept, study day) was used. Data from 245 patients evaluated at doses with a wide range of plasma concentrations (with 26% of data higher than mean Cmax at the 4 mg dose used in phase 3) had no meaningful effect on QTc based on model-predicted mean change in QTcF/QTcP from baseline. The predicted mean ΔΔQTcF and ΔΔQTcP (90% CI) at the geometric mean Cmax achieved with the 4 mg dose were 0.0710 msec (-0.221, 0.363) and 0.0591 msec (–0.242, 0.361), respectively. The upper limits of the 90% CIs for the mean ΔΔQTcF and mean ΔΔQTcP were well below 5 msec even at a plasma ixazomib concentration of 200 ng/mL (~ 4-times the geometric mean Cmax at the 4 mg dose). Also, less than 1% had QTc values greater than 480 msec and none of those data points were greater than 500 msec. Only 1 observation of ΔQTcP was greater than 60 msec and no such observations occurred for ΔQTcF. Less than 2 % of ΔQTcF and ΔQTcP data were greater than 30 msec. There was no clinically meaningful effect predicted on heart rate at a Cmax of 4 mg once-weekly dose.

In the pivotal study C16010, 360 patients in the ixazomib regimen and 360 patients in the placebo were evaluated for changes in QTcF and QTcB (Bazett's method). Most patients (~ 87% each arm) had a maximum post-dosing QTcF <450msec. Only 8 patients (3 in ixazomib/5 placebo) had a maximum post-dosing QTcF ≥500 msec. Increases from baseline in QTcF of ≥60 msec were observed in 6% and 3% of patients in the ixazomib and placebo regimens, respectively. Most patients (~ 76% each arm) had a maximum post-dosing QTcB <450msec. Only 26 patients (13 ixazomib/10 placebo) had a maximum post-dosing QTcB ≥500 msec. Increases from baseline were observed in 5% and 7% of patients in the ixazomib and placebo, respectively.

Exposure response

Exposure-response (E-R) analyses was performed on the basis of pivotal data to evaluate the relationship between ixazomib exposure and complete response (CR), very good partial response (VGPR), partial response (PR) and progression-free survival (PFS). The results of the logistic regression analyses showed that exposure was not a predictor for the clinical efficacy responses (CR vs ≤ VGPR, ≥ VGPR vs ≤ PR, and ≥ PR vs ≤ SD). In addition, exposure was not a significant predictor of PFS. After a median of 12 treatment cycles (maximum follow-up of 26 cycles) for this analysis, 80% of patients did not have an ixazomib dose reduction. Accordingly, the extent of inter-patient variability in time-averaged ixazomib exposure in the study population is limited largely to that resulting from inter-patient variability in apparent oral clearance.

An exposure-response analysis for PFS and best clinical response was conducted based on efficacy data from the pivotal study C16010. The exposure metric for ixazomib was time-averaged systemic exposure (AUC/day). Kaplan-Meier estimates for PFS in the ixazomib+LenDex regimen were stratified by 4 ixazomib exposure quartiles and compared to the placebo+LenDex regimen. Median PFS estimates in all exposure quartiles (range: 16.8-21.4 months) in the ixazomib+LenDex regimen were

longer than the median PFS estimate of 14.7 months for the control. There was a similar trend of the treatment effect in favour of ixazomib as the hazard ratios in all ixazomib exposure quartiles were <1 (range 0.646 -0.794). Ixazomib exposure at the 4 mg once weekly dose was not a significant predictor of PFS.

Exposure and best response rates (CR, ≥VGPR, and ≥PR) analysis also showed ixazomib exposure at the 4 mg once weekly dose was not a statistically significant predictor of clinical responses. After a median 12 treatment cycles (max 26 cycles) for this analysis, 80% of patients did not have an ixazomib dose reduction.

The MTD of once-weekly ixazomib in combination with a 28-day cycle of LenDex was established at 2.97 mg/m^2 (equivalent to 5.5 mg fixed dose). However, DLTs experienced in the dose-escalation cohorts overall included nausea, vomiting, syncope, rash, and peripheral neuropathy. Although the 2.97 mg/m^2 dose (equivalent to 5.5 mg fixed dose) of ixazomib was generally tolerable, it was noted that this ixazomib dose may compromise the dose of lenalidomide (ie, lead to dose reduction); the median dose intensity for lenalidomide was 84.6% and 96.0% for the 2.97 mg/m^2 (equivalent to 5.5 mg fixed dose) and 2.23 mg/m^2 (equivalent to 4 mg fixed dose) doses, respectively.

2.4.4. Discussion on clinical pharmacology

Ixazomib citrate was not detected in Sprague-Dawley rat, beagle dog, or human plasma samples spiked with high concentrations of ixazomib citrate (up to 29 µM). Instead, only a substantial peak corresponding to ixazomib was observed, indicating that ixazomib citrate rapidly and completely converts to ixazomib in plasma.

The bioanalysis of the nonclinical and clinical study samples used an ixazomib analytical reference standard, which is a mixture of its boroxine, free acid and oligomeric forms. Current methodology is unable to determine the exact percentage of the boroxine, free acid and oligomeric forms in the mixture for a given lot of material, and previous bioanalysis was conducted assuming 100% free boronic acid in the reference standard. Therefore, the maximum possible underestimation in results associated with assuming that the reference standard comprises 100% boronic acid (the free acid) is 5.3%; this potential underestimation is deemed not to have a meaningful impact on the bioanalytical results for the nonclinical and clinical studies.

In the ADME study, the mean total recovery of the administered radioactive dose was 84%, with 62% of the dose recovered in urine and 22% of the dose recovered in faeces. The mean urinary recovery of unchanged ixazomib in the urine was 3.2% of the administered dose.

The extent of faecal elimination does not suggest extensive elimination of unchanged drug and the renal elimination does not suggest active secretion therefore the involvement of any transporters, with the exception of hepatic uptake, in the elimination can probably be discounted.

The results of the ADME study are incomplete as metabolite identification of plasma, urine and faeces is not reported over a long enough time scale. The applicant was recommended to provide after authorisation information from the human ADME study on the drug related components in excreta post 7 days, preferably up to 20 days, by concentrating samples from the current study (however, the issues identified in the application currently prevent recommending to grant a marketing authorisation).

Metabolism appears to be a major route of elimination for ixazomib.

In an exploratory non-radiolabelled profiling clinical study using a semi-quantitative method, metabolite M8 was identified to be approximately 10% of the total drug-related exposure. In the

definitive radiolabelled human ADME study this metabolite was below the detection limit. Therefore on the basis of ICH S9 and ICH M3(R2) further characterization of M8 is not warranted. This is agreed however, characterisation of a further two unknown metabolites in human plasma is still ongoing and should be available in Q2 2016. The applicant was recommended to provide information from the human ADME study on the drug related components in plasma post 24 hours, by concentrating samples from the current study.

It is considered that the profiling of plasma and excreta is not adequate as the time periods are too short. Further profiling of plasma and excreta at later time points is required before any conclusion from this data can be endorsed. In case of a positive opinion the applicant is recommended to submit the final study report for identification of the most abundant human plasmatic metabolite P1 (that is expected to be completed by the end of the first half of 2016) together with available information on its qualification in plasma and excreta in non-clinical species, rat and dog.

The PK of ixazomib is similar in patients with normal hepatic function and in patients with mild hepatic impairment based on the results of a population PK analysis. The PK of ixazomib was characterized in patients with normal hepatic function at 4 mg (N=12), moderate hepatic impairment at 2.3 mg (total bilirubin > 1.5 3 x ULN, N=13) or severe hepatic impairment at 1.5 mg (total bilirubin > 3 x ULN, N=18). Unbound dose normalized AUC was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. Therefore, a reduced starting dose (3 mg) of ixazomib is recommended for patients with moderate or severe hepatic impairment.

The PK of ixazomib is similar in patients with normal renal function and in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min) based on the results of a population PK analysis. The PK of ixazomib was characterized at a dose of 3 mg in patients with normal renal function (creatinine clearance ≥ 90 mL/min, N=18), severe renal impairment (creatinine clearance < 30 mL/min, N=14), or ESRD requiring dialysis (N=6). Unbound AUC is 39% and 34% higher respectively in patients with severe renal impaired patients and those with ESRD than in those with normal function. Therefore, a reduced starting dose of ixazomib (3 mg) is recommended in these groups of patients. Pre- and post dialyzer concentrations of ixazomib measured during the haemodialysis session were similar, suggesting that ixazomib is not dialyzable.

There was no clinically meaningful effect of age (23- 91 years), sex, body surface area (1.2 2.7 m2), or race on the clearance of ixazomib based on the results of a population PK analysis.

Race was not identified as a statistically significant covariate in the population PK analysis. In addition, the individual predicted exposures following a single 4 mg ixazomib dose were calculated using the final model. There was no clinically meaningful difference in AUC (<20%) between Whites and Blacks. However, the median AUC was 35% higher in Asian patients than in Whites although there was an overlap in AUC across the two race groups. Despite the modestly higher AUC in Asian patients, exposures achieved after a 4 mg weekly dose are not expected to exceed those observed at the Western MTD (ie, 5.5 mg). Based on these considerations, and considering that the adverse events following ixazomib treatment are monitorable, reversible and manageable through protocol-specified dose modification guidelines, no prospective starting dose adjustment is proposed for Asian patients. Patients across races, including patients enrolled in Asian countries, are being administered a common global dose of ixazomib in the ongoing phase 3 clinical program, including Study C16010.

Co administration of ixazomib with clarithromycin, a strong CYP3A inhibitor, did not result in a clinically meaningful change in the systemic exposure of ixazomib. Ixazomib Cmax was decreased by 4% and AUC was increased by 11%. Therefore, no dose modification is required for ixazomib with co administration of strong CYP3A inhibitors.

Co administration of ixazomib with strong CYP1A2 inhibitors did not result in a clinically meaningful change in the systemic exposure of ixazomib based on the results of a population pharmacokinetic (PK) analysis. Therefore, no dose modification is required for ixazomib with co administration of strong CYP1A2 inhibitors.

Co administration of ixazomib with rifampicin decreased ixazomib Cmax by 54% and AUC by 74%. Therefore, co administration of strong CYP3A inducers with ixazomib is not recommended.

Ixazomib is not a reversible or a time dependent inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity or corresponding immunoreactive protein levels. Ixazomib is not expected to produce drug drug interactions via CYP inhibition or induction.

Ixazomib is a low affinity substrate of P gp. Ixazomib is not a substrate of BCRP, MRP2 or hepatic OATPs. Ixazomib is not an inhibitor of P gp, BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2 K. Ixazomib is not expected to cause transporter mediated drug drug interactions.

The effect of ixazomib on the PK of lenalidomide and dexamethasone has not been directly studied. Lenalidomide undergoes minimal metabolism and is predominantly renally cleared. In addition, in vitro studies using human liver microsomes, recombinant CYPs, and human hepatocytes showed that lenalidomide is not a substrate of CYP enzymes. Lenalidomide is a weak substrate of P-gp, and is not a substrate of BCRP, MATE1, MRP1. MRP2, MRP3, OAT1, OAT3, OATP1B1, OCT1, OCT2, organic cation transporter, novel type 1 and 2 (OCTN1, and OCTN2) based on in vitro studies. In a clinical study, no significant changes in lenalidomide PK were observed when coadministered with the P-gp inhibitor, quinidine; thereby, suggesting that P-gp mediated transport is not a significant contributor to lenalidomide clearance in the clinical setting.

When ixazomib is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of oral contraceptives needs to be considered. Women using hormonal contraceptives should additionally use a barrier method of contraception.

The inhibition of 20S proteasome activity in whole blood after once-weekly and twice-weekly IV bolus dosing in clinical studies indicated maximum activity within 30 minutes in most patients, a dose-dependent profile and a reversible inhibition effect.

Non clinical and clinical studies have excluded a potential effect of ixazomib in QTc. Clinical safety data showed a profile of increased gastro-intestinal toxicity with the triple combination, mainly nausea, vomiting and diarrhoea. Although peripheral neuropathy was also reported in clinical studies in common with other proteasome inhibitors, in the majority of cases was of low grade.

Data from the pivotal study on exposure-effect using the proposed ixazomib oral weekly dosing at 4 mg in combination with lenalidomide and dex showed consistent efficacy in terms of PFS and clinical response despite any potential variability in exposure. There is no data on exposure-effect using different doses of ixazomib.

2.4.5. Conclusions on clinical pharmacology

The pharmacology of ixazomib has been adequately investigated.

2.5. Clinical efficacy

2.5.1. Dose response studies

The selection for the Phase 3 dose and schedule of ixazomib was based on data from two phase 1 single-agent studies (C16004 and C16003) and one phase 1/2 combination study with Lendex (C16005).

Dose schedule (Studies C16004 and C16003)

Studies C16003 and C16004 were phase 1, open-label, multi-centre (in US), dose-escalation studies evaluating the safety, maximum tolerated dose (MTD) and activity of single-agent oral ixazomib in adult patients with RRMM. The patients treated during the dose-escalation part had relapsed after receiving at least 2 prior lines of therapy that had to include some combination of bortezomib, immunomodulatory drugs (IMiDs), and corticosteroids. After determination of the MTD, additional patients were enrolled in 1 of 4 MTD expansion cohorts.

The studies differed in dosing schedule:

- C16004, ixazomib orally once weekly, Days 1, 8, and 15 of a 28 day cycle (the same ixazomib schedule used in pivotal study C16010).
- C16003, ixazomib orally twice weekly, Days 1, 4, 8, and 11 of a 21-day cycle.

Dosing started in both studies at 0.24 mg/m^2 BSA based on non-clinical studies and escalated to equivalent of 4 mg fixed dose in Study C16003:

Table 24. Dosing schedule Study C16003

BSA	Fixed
0.24 mg/m^2	0.45 mg
0.48 mg/m^2	1 mg
0.8 mg/m^2	1.5 mg
1.2 mg/m^2	2.2 mg
1.68 mg/m^2	3 mg
2.0 mg/m^2	3.7 mg
2.23 mg/m^2	4 mg

In C16004, dose escalation continued to 2.97 mg/m^2 (~5.5 mg fixed dosing) and 3.95 mg/m^2 (~7 mg fixed dose). The MTD was identified as 2.97 mg/m^2 in C16004 and 2 mg/m^2 (~ 3.7 mg fixed dosing) in C16003.

Once the MTD was established, patients were enrolled into the 4 expansion cohorts on the basis of their disease status and prior therapy: Relapsed and Refractory (refractory to most recent therapy); PI-Naive (relapsed or refractory); Velcade-Relapsed (relapsed after previous bortezomib but were not refractory to it); Carfilzomib cohort (relapsed or refractory and previously exposed to carfilzomib). If a patient met the criteria for both the Relapsed and Refractory cohort and Velcade-Relapsed cohort, then the patient was enrolled in the Relapsed and Refractory MTD expansion cohort unless the cohort was full, in which case the patient was then enrolled in the Velcade-Relapsed.

Disease response was assessed by the investigators using the IMWG criteria with the addition of MR from the EBMT criteria. Response assessments were performed every other treatment cycle beginning with Cycle 3, Day 1. The efficacy analysis was based on the ORR (CR+PR) and CR+PR+MR rate. Patients discontinued treatment if they experienced PD or unacceptable toxicity. The maximum duration of treatment was 12 cycles unless it was determined that a patient would benefit from continued therapy. Patients were followed for 30 days after the last dose of ixazomib or until the start of subsequent antineoplastic therapy.

Sixty patients were enrolled in each study and the expansion cohorts included 31 patients in C16004 and 40 patients in C16003. The median overall treatment duration in the safety population of C16004 was 53.5 days (range, 1–324 days) and of C16003 was 70.5 days (range, 1–911 days).

The phase 1 studies included heavily pre-treated patients representative of patients with RRMM for whom few treatment options remain. Ixazomib demonstrated activity among these patients. A heterogeneous group of 19 patients in the phase 1 studies responded to ixazomib treatment with at least MR, with 17 patients achieving a PR or better. The responders ranged in age from 51 to 83 years, they had between 2 and 12 prior lines of therapy, 4 patients had high-risk cytogenetic abnormalities, and 4 patients had ISS Stage III myeloma. Among the 19 responders, 11 patients were refractory to lenalidomide and 9 patients were refractory to PIs, 5 of whom were also refractory to lenalidomide.

A summary of the results is presented in Table 25.

Table 25. Comparison of Efficacy and Safety between C16003 (Twice-Weekly Dosing) and C16004 (Once-Weekly Dosing)

	C16003 (N=60)		**C16004 (N=60)**	
Dose schedule	**Twice Weekly** (Days 1, 4, 8, and 11 of a 21-day cycle)		**Once Weekly** (Days 1, 8, and 15 of a 28-day cycle)	
MTD	2 mg/m^2 (3.7 mg fixed dose)		2.97 mg/m^2 (5.5 mg fixed dose)	
	Total	**MTD-Expansion Cohort**	**Total**	**MTD-Expansion Cohort**
Response evaluable	N=55	N=39	N=50	N=30
ORR (CR+PR) – best response, confirmed or unconfirmed	8 (15%)	6 (15%)	9 (18%)	8 (27%) Including 2 patients with del(17) and 2 with t (4;14)
Safety population	N=60	N=40	N=60	N=31
Grade 3 TEAE	45 (75%)	31 (78%)	37 (62%)	24 (77%)
Grade 4 TEAE	23 (38%)	19 (48%)	13 (22%)	11 (35%)
Dose modification	36 (60%)	27 (68%)	27 (45%)	18 (58%)
Discontinuation due to TEAE	8 (13%)	8 (20%)	7 (12%)	4 (13%)

The response rates were similar between the 2 studies in whole study populations but MTD-expansion cohort had a higher ORR in C16004 than C16003 (27% vs 15%) and a similar median duration of response (PR or better) (5.6 months vs 5.7 months).

DLTs included nausea, vomiting, diarrhoea and rash in C16004 and rash and thrombocytopenia (borderline) in C16003. The incidences of Grade 3 and Grade 4 TEAEs were lower in the overall population in C16004 than in C16003 (Grade 3, 62% vs 75%; Grade 4, 22% vs 38%). At the MTD, the incidences of Grade 3 TEAEs were similar in C16004 and C16003, but the incidence of Grade 4 TEAEs was lower in C16004 than in C16003 (35% vs 48%). Also incidence of dose modifications due to AEs

was lower in C16004 overall population (45% vs 60%) and in the MTD-expansion cohort (58% vs 68%). Although the incidences of drug discontinuation due to AEs were similar in the overall C16004 and C16003 populations, in the MTD-expansion cohorts, more patients experienced TEAEs that led to drug discontinuation in C16003 than in C16004 (20% vs 13%).

In summary, in the MTD-expansion cohorts, the higher response rate and better tolerability with the once weekly ixazomib dose schedule supported selecting this schedule for phase 3 study. Additionally, once weekly ixazomib in a 28-day cycle combines seamlessly with the 28-day LenDex treatment cycle, without compromising the LenDex schedule and dose intensity.

Dose in combination with Lendex (Study C16005)

Study C16005 was an open-label, multicentre clinical trial evaluating ixazomib oral in combination with Lendex in patients with newly diagnosed MM (NDMM).

The study consisted of a phase 1 dose-escalation part, to determine the MTD/RP2D of ixazomib in combination with Lendex and a phase 2, dose-expansion portion in which patients were treated at the RP2D.

In both phases, all treatments were given orally in repeated 28-day cycles. The regimen consisted of:

1) Induction (up to 12 cycles)

Ixazomib once weekly for 3 weeks (Days 1, 8, and 15) + Dex 40 mg (Days 1, 8, 15, 22) + Len 25 mg (Days 1-21)

Phase 1: ixazomib dose-escalation starting dose 1.68 mg/m^2, MTD 2.97 mg/m2 m^2(= 5.5 mg).

Phase 2: ixazomib at RP2D, 4.0 mg fixed dose

2) Maintenance (Cycle 13 and beyond)

For patients with ≥ SD, continue on single-agent ixazomib once weekly for 3 weeks (Days 1, 8, 15) in 28 day cycles at dose tolerated at end of induction phase.

Treatment would continue until PD or unacceptable toxicity. Sixty five patients with NDMM (excluding those with ≥ Grade 2 peripheral neuropathy) were enrolled (15 in phase 1 and 50 in phase 2). The study is still ongoing.

In phase 1, patients were dosed on the basis of their assigned cohort and received escalating (3+3 scheme) BSA-based doses (1.68, 2.23, 2.97, and 3.95 mg/m^2) of oral ixazomib. The MTD of once-weekly ixazomib in combination with a 28-day cycle of LenDex was established at 2.97 mg/m^2 (= 5.5 mg fixed dose). However, the median dose intensity for lenalidomide was 84.6% and 96.0% for the 2.97 mg/m^2 (5.5 mg) and 2.23 mg/m^2 (4 mg) doses, respectively. Among 3 patients treated at 2.23 mg/m^2 (4 mg), the outcome included two CR and one PR. Among the 6 patients treated at 2.95 mg/m^2 (5.5 mg) two achieved CR (including 1 sCR), three VGPR, and one PR.

The phase 2 portion began after determination of the MTD and evaluation of the safety at the MTD in at least 6 patients. The RP2D in this study was established as 2.23 mg/m^2 (=fixed dose of 4 mg).

As the once-weekly 4 mg dose of ixazomib in 28 day cycles, in combination with standard doses of LenDex was well tolerated and achieved an overall response rate of 90% it was chosen as the ixazomib dose to be given in combination with LenDex in the phase 3 study.

2.5.2. Main study

Study C16010

This is an ongoing phase 3, randomized, double-blind, multicenter clinical trial comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or refractory multiple myeloma.

Methods

Study Participants

Inclusion criteria

- Male or female patients 18 years of age or older.
- Patients must have had measurable MM disease with at least serum M-protein ≥1 g/dL or urine M-protein ≥200 mg/24 hours or FLC level ≥10 mg/dL if the serum FLC ratio was abnormal
- Patients with RRMM who had received 1 to 3 prior therapies including:
  - relapsed from previous treatment(s) but were not refractory to any previous treatment
  - refractory to all lines of previous treatment(s)
  - relapsed from at least 1 previous treatment AND additionally were refractory to at least 1 previous treatment.

[Note: Refractory disease was defined as disease progression on treatment or progression within 60 days after the last dose of a given therapy. Patients who progressed after 60 days from the last dose of a given therapy were considered relapsed.]

- Absolute neutrophil count (ANC) ≥ 1000/mm^3 and platelet count ≥ 75,000/mm^3
- Total bilirubin ≤ 1.5 ULN
- ALT and AST ≤ 3 ULN
- Calculated creatinine clearance ≥ 30 mL/min (if ≤ 60 ml/min were to receive a reduced dose of lenalidomide that could be increased depending on tolerability and response to treatment)
- ECOG performance status of 0, 1, or 2
- Patients who received prior allogenic transplant must have had no active GVHD
- Postmenopausal or surgically sterile female patients. Male patients and female patients of childbearing potential able to adhere to protocol measures for prevention pregnancy.
- Able to receive prophylactic anticoagulation (aspirin or enoxaparin). For patients with prior history of deep vein thrombosis low-molecular weight heparin was mandatory.

Exclusion criteria

- Refractory to lenalidomide or proteasome inhibitor-based therapy at any line.
- Breastfeeding or pregnancy
- Major surgery, radiotherapy or infection requiring antibiotics or serious infection within 14 days before randomization
- Central nervous system involvement

- Waldenstrom's macroglobulinemia, POEMS syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome
- Current uncontrolled cardiovascular conditions or myocardial infarction within 6 months before randomization
- Systemic treatment with strong inhibitors of cytochrome P450 (CYP) 1A2 (CYP1A2), strong inhibitors/inducers of CYP3A or use of Ginkgo biloba or St. John's wort within 14 days before randomization
- Ongoing or active systemic infection, active hepatitis B or C virus infection, or known HIV positive.
- Comorbid illnesses or other severe concurrent disease which, according to the investigator, would make the patient inappropriate for entry (e.g., peripheral neuropathy that is Grade 1 with pain or Grade 2 or higher of any cause).
- Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and any evidence of residual disease (except non-melanoma skin cancer and carcinoma in situ of any type that had undergone complete resection).

Treatments

Patients were randomized (1:1) to receive oral [ixazomib+LenDex] or [placebo+LenDex] at home in 28-days cycles until progressive disease (PD) or unacceptable toxicity, whichever occurred first:

- Ixazomib 4 mg or matching placebo capsule on Days 1, 8, and 15
- Lenalidomide 25 mg on Days 1 through 21
- Dexamethasone 40 mg on Days 1, 8, 15, and 22

Patients with a low creatinine clearance ≤60 mL/min (or ≤50 mL/min, according to lenalidomide prescribing information/local practice) received a reduced lenalidomide dose of 10 mg once daily on Days 1 -21 but could be increased to 15 mg after 2 cycles if the patient was not responding to treatment and was able to tolerate it. If renal function normalized and the patient continued to tolerate this treatment, lenalidomide could be escalated to 25 mg.

Dose modifications of 1 or multiple agents were made based on toxicities and followed pre-specified criteria.

Concomitant medications allowed included myeloid growth factors, erythropoietin (use to be minimized due to potential risk of DVT when given concurrently with lenalidomide), digoxin and bisphosphonates. Palliative radiotherapy for pain control of a pre-existing lesion could be allowed after discussion with clinician.

Objectives

The primary objective of this study was to determine whether the addition of oral ixazomib to the background therapy of lenalidomide and dexamethasone improves PFS in patients with RRMM.

Key secondary objectives included the evaluation of overall survival (OS) and the OS in high-risk patients carrying deletion del (17).

Other secondary objectives included the evaluation of: Overall response rate (ORR), including partial response (PR), very good partial response (VGPR), and complete response (CR); CR+VGPR; Duration of response (DOR); time to progression (TTP); safety of the addition of ixazomib to lenalidomide and dexamethasone; pain response rate, as assessed by the Brief Pain Inventory–Short Form (BPI-SF) and analgesic use; change in global health status, functioning, and symptoms as measured by the patient-reported outcome (PRO) instrument European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and MY-20 module; PFS and OS in high-risk cytogenetic patient groups such as translocations t(4;14), t(14;16), +1q, del(13), or del(17); potential relationship between response or resistance to ixazomib treatment and proteasome and NF-kB-related genes, such as tumour necrosis factor receptor-associated factor-3 (TRAF-3), in blood samples and pharmacokinetic (PK) analyses (collection of PK data).

Outcomes/endpoints

The primary efficacy 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, or death due to any cause, whichever occurred first.

Secondary efficacy endpoints

Overall Survival (OS) defined as the time from the date of randomization to the date of death;

Overall survival within the high-risk patients carrying del(17) subgroup (patients reported as positive for del(17) by the central laboratory combined with those cases that lacked a central laboratory result and were reported positive by the local laboratory) was defined the same as OS in the ITT population;

Overall response rate (ORR): defined as the proportion of ITT patients who achieved PR or better;

Complete Response (CR) and Very Good Partial Response (VGPR) rate;

Duration of response (DOR): measured as the time from the date of first documentation of response to the date of first documented progression;

Time to progression (TTP): measured as the time from randomization to the date of first documented progression.

Pain response rate, measured by the proportion of pain responders, pain response was defined as the occurrence of a 30% reduction from baseline in BPI-SF worst pain score over the last 24 hours without an increase in analgesic use at 2 consecutive evaluations. Pain response rate was analyzed in patients in the ITT population with a baseline pain score ≥ 4.

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(17), t(4;14), or t(14;16);

Association between response or resistance to Ixazomib treatment and proteasome and NFKB-related genes, such as TRAF-3, or circulating proteasome levels;

Association between response or resistance to Ixazomib treatment and mutations in key pathways, such as RAS/RAF and PI3K;

Plasma concentration-time data to contribute to future population PK analysis.

Sample size

The sample size calculation was based on the secondary endpoint of OS. Approximately 703 patients were planned to be enrolled based on a calculation on OS with a 2-sided test at the significance level of α=0.05, power of 80%, assuming median OS in the control of 30 months versus experimental arm of 39 months (HR 0.77), and around 10% dropout rate. The final analysis of OS was estimated to occur approximately 80 months from the enrolment of first patient. With an observed HR of 0.833 (e.g., median OS of 30 months for control vs 36 months for treatment, 20% improvement), statistical significance could be claimed at the final analysis with 486 death events.

Randomisation

Patients were randomized in a 1:1 ratio into 1 of the 2 treatment arms: ixazomib or matching placebo capsules in combination with LenDex.

Patients were stratified by: 1 versus 2 or 3 prior therapies; PI-exposed versus PI-naïve and ISS Stage at screening of I or II versus III.

Blinding (masking)

This was a double blind study.

Statistical methods

The analysis of the primary endpoint, PFS, was based on the ITT population using IRC-assessed progression data. PFS was to be analyzed when 262 and 365 PFS events had occurred for the first interim analysis and second interim analysis, respectively. A 2-sided, stratified log-rank test was to be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.0163 and 0.0337 for the first and the second interim analysis, which corresponded to a nominal p value of 0.0451 based on O'Brien-Fleming stopping boundary (the Lan-DeMets method). In addition, an unadjusted stratified Cox model was used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan Meier (K-M) survival curves and K-M medians (if estimable), along with their 2-sided 95% CIs, were also provided for each treatment group.

Sensitivity analyses for the primary endpoint, PFS, included: PFS assessed by investigator in the ITT population, PFS assessed by IRC in the PP population, PFS assessed by IRC using different censoring mechanisms in the ITT population based on both FDA and EMA guidance (for example, not censoring for patients who discontinued treatment and underwent transplant or received alternative neoplastic therapy). Furthermore, a stepwise Cox model was implemented to identify potential predictive factors using relevant demographic or diagnostic covariates, with the entry level fixed at 0.25 and a stay level fixed at 0.10. In addition to treatment and stratification factors, the model may have included, but was not limited to, the following prognostic factors: age; race (white; non-white); prior therapy (IMiD-exposed vs IMiD-naïve); baseline ECOG score; cytogenetic test (high risk vs normal); and corrected serum calcium.

Subgroup analyses were performed for PFS relative to baseline stratification factors, demographic data such as sex, race and age, and disease characteristics such as type of prior regimen.

Analysis Populations

Four different patient populations were defined.

- Intent-to-Treat (ITT) population: defined as all patients who were randomized. Patients were analysed according to the treatment they were randomized to receive, regardless of any errors of dosing.

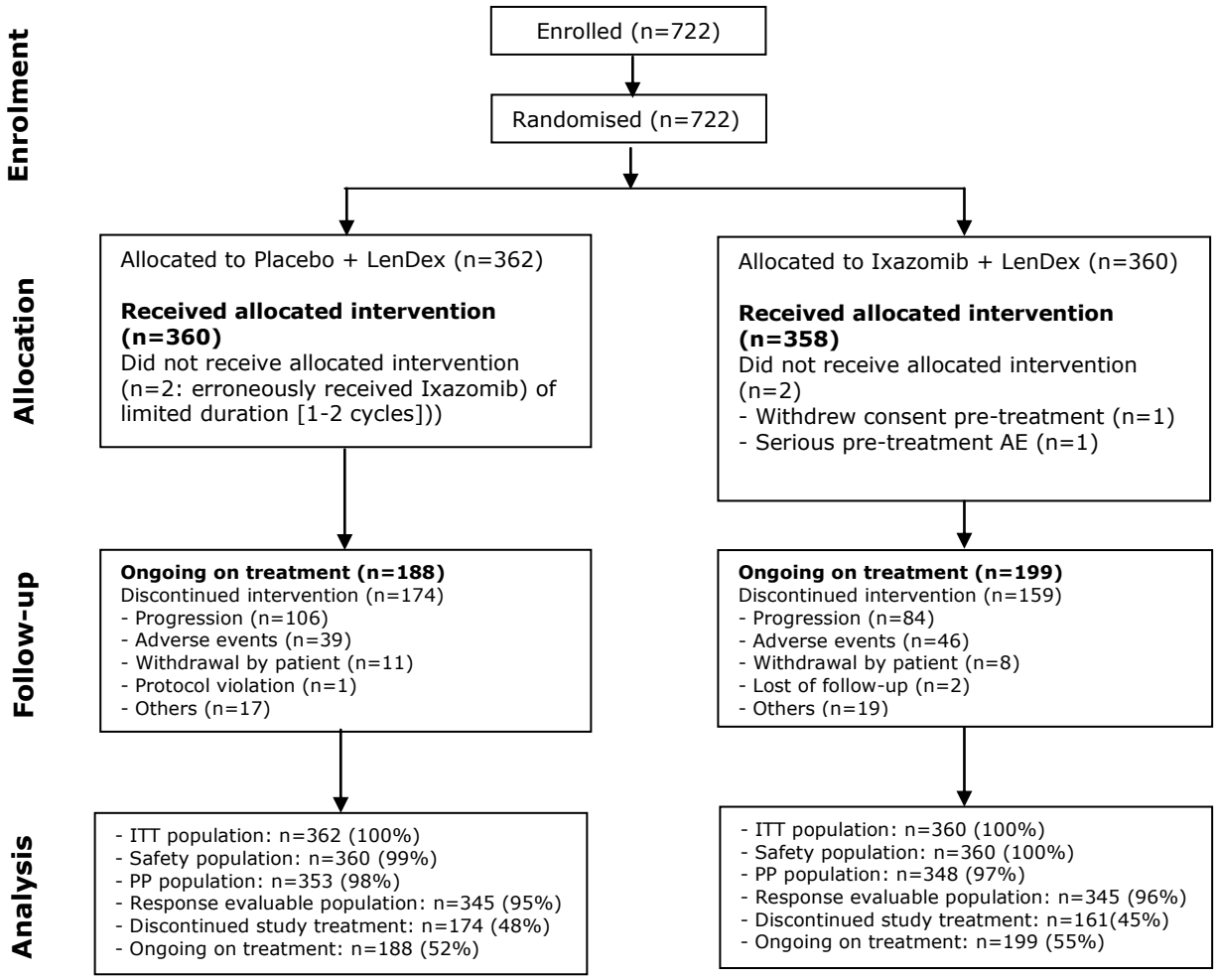
- Safety population: defined as all patients who received at least 1 dose of any study drug. Patients were analysed according to the treatment actually received.

- Response-Evaluable population: defined as patients who received at least 1 dose of study drug, had measurable disease at baseline, and had at least 1 post-baseline response assessment.

- Per-Protocol (PP) population: defined as patients who did not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the study clinician, who was blinded to study drug assignment. All decisions to exclude patients from the PP population were made before the unblinding of the study.

Results

Participant flow



Recruitment

Between 28 August 2012 and 27 May 2014, a total of 722 patients were randomized at 147 study centres in 26 countries. A total of 224 patients were from Western countries (North America and West Europe) and 498 patients were from non-Western countries. The countries with the largest number of patients were France (11%), New Zealand (9%) and the US (7%). By region, 483 patients (67%) were

enrolled from 91 sites in Europe, 143 (20%) from 35 sites in the Asia-Pacific (APAC) region, and 96 (13%) from 21 sites in North America (NA).

Conduct of the study

The original protocol was finalized on 21 February 2012 and was followed by Amendment 1 (14 September 2012), Amendment 2 (China only), Amendment 3 (8 July 2014), and Amendment 4 (China only).

One hundred thirty-eight patients were enrolled under the original protocol and 584 patients under Amendment 1. An update of the IMWG response criteria version from 2006 to 2011 was part of the amendment 1.

Amendment 3 included an update of the statistical analyses to include the assumptions on PFS for sample size calculation and additional interim analysis, and also to remove the non-inferential test on PFS at the original planned second interim analysis. This amendment was in place prior to the first interim analysis and prior to breaking the treatment blind to the internal submission working team; no changes were made to the statistical analysis plan after unblinding.

As the definition of high-risk abnormalities for MM evolved on the basis of new data, the cytogenetic abnormalities of del(13) and +1q were no longer considered to be high-risk abnormalities and were excluded from the high-risk evaluations in the final SAP.

Protocol compliance

Table 26. Major Protocol Deviations (Safety Population - Study C16010)

	Placebo+LenDex N=360	Ixazomib+LenDex N=360	Total N=720
Patients with at least 1 major protocol deviation	14 (4)	18 (5)	32 (4)
Investigational product (IP) compliance ≤70%	8[a] (2)	7[b] (2)	15 (2)
Inclusion/exclusion issues	6[a] (2)	7 (2)	13 (2)
Excluded concomitant medication taken	1 (<1)	4[b] (1)	5 (<1)
Major overdose error			1 (<1)
No pregnancy test			1 (<1)

Note: Shaded cells denote data removed to protect the scientific integrity of this ongoing blinded trial.
a Two patients had 2 deviations: inclusion/exclusion issues and IP issues.
b One patient had 2 deviations: excluded medication taken and IP issues.

Baseline data

Table 27. Demographics and Stratification Factors (ITT Population- Study C16010)

Parameter	Placebo+LenDex N=362	Ixazomib+LenDex N=360	Total N=722
Age (years)			
Mean (std dev)	65.8 (9.70)	65.5 (9.13)	65.7 (9.41)
Median	66.0	66.0	66.0
Minimum, maximum	30, 89	38, 91	30, 91
Age Categories (years), n (%)			
≤65	176 (49)	168 (47)	344 (48)
>65-≤75	125 (35)	145 (40)	270 (37)
>75	61 (17)	47 (13)	108 (15)
Sex, n (%)			
Male	202 (56)	207 (58)	409 (57)
Female	160 (44)	153 (43)	313 (43)
Race, n (%)			
White	301 (83)	310 (86)	611 (85)
Black or African American	6 (2)	7 (2)	13 (2)
Native Hawaiian/Other Pacific Islander	2 (<1)	2 (<1)	4 (<1)
Asian[a]	34 (9)	30 (8)	64 (9)
Other	4 (1)	4 (1)	8 (1)
Not reported	15 (4)	7 (2)	22 (3)
Ethnicity, n (%)			
Hispanic or Latino	12 (3)	9 (3)	21 (3)
Not Hispanic or Latino	333 (93)	339 (95)	672 (94)
Not reported	15 (4)	10 (3)	25 (3)
Missing	2	2	4
Stratification factors:			
Lines of prior therapy			
1	213 (59)	212 (59)	425 (59)
2 or 3	149 (41)	148 (41)	297 (41)
Proteasome inhibitor			
Exposed	253 (70)	250 (69)	503 (70)
Naïve	109 (30)	110 (31)	219 (30)
ISS Stage at screening[b]			
Stage I or Stage II	318 (88)	314 (87)	632 (88)
Stage III	44 (12)	46 (13)	90 (12)

a The 64 Asian patients included 41 Japanese, 10 Chinese, 6 Korean, 5 "other" Asians, 1 Asian Indian, and 1 Asian whose country was not reported.

b Stage I: Serum β2-microglobulin <3.5 mg/L and albumin ≥3.5 g/dL; Stage II: Neither Stage I or III, meaning that either: β2-microglobulin level ≥3.5 and <5.5 mg/L (with any albumin level), OR albumin <3.5 g/dL with β2-microglobulin <3.5 mg/L; Stage III: Serum β2-microglobulin ≥5.5 mg/L.Normal serum β2-microglobulin: <3.0 mg/L; normal albumin: 3.5–5.0 g/dL.

Table 28. Prior Therapy (ITT Population- Study C16010)

Parameter	Placebo+LenDex N=362	Ixazomib+LenDex N=360	Total N=722
Line of prior therapy (based on sponsor review),[a] n (%)			
1	217 (60)	224 (62)	441 (61)
2	111 (31)	97 (27)	208 (29)
3	34 (9)	39 (11)	73 (10)
Patient population categories, n (%)Table 29. Prior Therapy (ITT Population- Study C16010)	(n=362)	(n=359)	(n=721)
Relapsed patients[b]	280 (77)	276 (77)	556 (77)
Refractory patients[c]	40 (11)	42 (12)	82 (11)
Refractory and relapsed patients[d]	42 (12)	41 (11)	83 (11)
Type of prior regimens, n (%)			
Prior proteasome inhibitor (PI) therapy exposed	253 (70)	249 (69)	502 (70)
Refractory to any prior PI therapy[e]	17 (7)	22 (9)	39 (8)
Bortezomib (VELCADE) contained	250 (69)	248 (69)	498 (69)
Carfilzomib contained	4 (1)	1 (<1)	5 (<1)
Prior IMiD therapy exposed	204 (56)	193 (54)	397 (55)
Refractory to any prior IMiD therapy[e]	50 (25)	41 (21)	91 (23)
Lenalidomide contained	44 (12)	44 (12)	88 (12)
Thalidomide contained	170 (47)	157 (44)	327 (45)
Thalidomide refractory	49 (14)	40 (11)	89 (12)
Corticosteroid contained	355 (98)	356 (99)	711 (98)
Dexamethasone	298 (82)	302 (84)	600 (83)
Prednisone	117 (32)	117 (33)	234 (32)
Melphalan contained	291 (80)	293 (81)	584 (81)
Other	250 (69)	248 (69)	498 (69)
Type of last prior regimen, n (%)			
Bortezomib (VELCADE) contained	189 (52)	185 (51)	374 (52)
Thalidomide contained	113 (31)	103 (29)	216 (30)
Thalidomide refractory	27 (7)	29 (8)	56 (8)
Lenalidomide contained	34 (9)	32 (9)	66 (9)
Corticosteroid contained	308 (85)	294 (82)	602 (83)
Dexamethasone	234 (65)	228 (63)	462 (64)
Prednisone	84 (23)	76 (21)	160 (22)
Carfilzomib contained	4 (1)	1 (<1)	5 (<1)
Melphalan contained	179 (49)	197 (55)	376 (52)
Other	179 (49)	171 (48)	350 (48)
Best response to prior therapy, n (%)	(n=362)	(n=359)	(n=721)
Complete response	117 (32)	123 (34)	240 (33)
Partial response	210 (58)	198 (55)	408 (57)
Stable disease	15 (4)	19 (5)	34 (5)
Progressive disease	11 (3)	8 (2)	19 (3)
Unable to assess			4 (<1)
Primary refractory patients,[f] n (%)	22 (6)	24 (7)	46 (6)

Table 28. Prior Therapy (ITT Population- Study C16010)

Parameter	Placebo+LenDex N=362	Ixazomib+LenDex N=360	Total N=722
Patient relapsed on last prior therapy, n (%)	300 (83)	294 (82)	594 (82)
Patient refractory on last prior therapy, n (%)	55 (15)	59 (16)	114 (16)
Time since last dose of prior therapy to first dose of study drug (months)			
Median	13.2	14.5	14.0
Minimum, maximum	0, 203	0, 113	0, 203
Time since disease progression on prior therapy to first dose at study entry (months)	(n=362)	(n=359)	(n=721)
Median	2.2	2.3	2.3
Minimum, maximum	1, 63	0, 85	0, 85
Patients with stem cell transplant, n (%)	199 (55)	212 (59)	411 (57)
Allogenic	4 (2)	6 (3)	10 (2)
Autologous	193 (97)	202 (95)	395 (96)
Both	2 (1)	4 (2)	6 (1)
Time since last transplant to first dose at study entry (months)	(n=199)	(n=212)	(n=411)
Mean (std dev)	44.5 (33.36)	43.0 (31.99)	43.8 (32.62)
Median	35.9	34.7	35.3
Min, Max	3, 231	3, 156	3, 231

Note: Shaded cells denote data removed to protect the scientific integrity of this ongoing blinded trial.
a Prior therapies were defined per Rajkumar et al. 2011; may not exactly match the stratification factor (lines of prior therapy: 1 versus 2 or 3).
b Relapsed was defined as patients who relapsed from at least 1 previous treatment (>60 days after the last dose of treatment) but were not refractory to any previous treatment.
c Refractory was defined as patients who had disease progression on treatment or progression within 60 days after the last dose of at least 1 previous treatment but were not relapsed to any previous treatment; patients who were refractory to lenalidomide or proteasome inhibitor-based therapy were to be excluded.
d Refractory and relapsed was defined as patients who relapsed from at least 1 previous treatment and additionally were refractory to at least 1 previous treatment.
e Note that blinded medical review of patients refractory to any prior PI or IMID therapy was also done and classified fewer patients as refractory.
f Primary refractory patients were those with PD or SD as best response (never responded) across all lines ofprior therapy. Patients with both PD and SD were counted in the PD category.

Table 30. Key Baseline Disease Characteristics (ITT Population - Study C16010)

Parameter	Placebo+LenDex N=362	Ixazomib+LenDex N=360	Total N=722
Type of myeloma at study entry, n (%)			
IgG	199 (55)	198 (55)	397 (55)
Kappa	135 (37)	131 (36)	266 (37)
Lambda	62 (17)	66 (18)	128 (18)
Missing	2	1	3
IgA	48 (13)	76 (21)	124 (17)
Kappa	34 (9)	49 (14)	83 (12)
Lambda	14 (4)	27 (8)	41 (6)
Biclonala	17 (5)	13 (4)	30 (4)
Free Kappa light chains (no heavy chain), n (%)	53 (15)	37 (10)	90 (12)
Free Lambda light chains (no heavy chain), n (%)	41 (11)	35 (10)	76 (11)
Unable to classify[b]	3 (<1)	1 (<1)	4 (1)
ISS Stage at study entry, n (%)			
I	233 (64)	226 (63)	459 (64)
II	87 (24)	89 (25)	176 (24)
III	42 (12)	45 (13)	87 (12)
ECOG performance status, n (%)			
0	170 (47)	180 (50)	350 (48)
1	164 (45)	156 (43)	320 (44)
2	24 (7)	18 (5)	42 (6)
Missing	4 (1)	6 (2)	10 (1)
Serum creatinine (mg/dL)[c]	(n=361)	(n=360)	(n=721)
Median	0.9	0.9	0.9
Minimum, maximum	0, 2	0, 3	0, 3
≤2 mg/dL	356 (98)	355 (99)	711 (98)
Creatinine clearance (mL/min)[c]	(n=361)	(n=360)	(n=721)
Mean (std dev)	81.7 (31.63)	83.0 (30.01)	82.3 (30.82)
Median	78.4	78.4	78.4
Minimum, maximum	27, 233	20, 233	20, 233
<30 mL/min, n (%)	5 (1)	5 (1)	10 (1)
30–<60 mL/min, n (%)	95 (26)	74 (21)	169 (23)

Parameter	Placebo+LenDex N=362	Ixazomib+LenDex N=360	Total N=722
60-<90 mL/min, n (%)	129 (36)	155 (43)	284 (39)
≥90 mL/min, n (%)	132 (36)	126 (35)	258 (36)
Corrected calcium (mmol/L)[c]	(n=361)	(n=360)	(n=721)
Median	2.324	2.328	2.325
Minimum, maximum	1.95, 3.45	1.87, 4.43	1.87, 4.43
Baseline hemoglobin (g/L)[b]			
Median	115.0	116.0	115.0
Minimum, maximum	71, 167	68, 170	68, 170
Skeletal survey findings, n (%)	(n=329)	(n=330)	(n=659)
Within normal limits	44 (12)	43 (12)	87 (12)
Abnormal	285 (79)	287 (80)	572 (79)
Lytic bone lesions present (skeletal survey), n (%)	(n=329)	(n=330)	(n=659)
Yes	221 (67)	231 (70)	452 (69)
No	100 (31)	95 (29)	195 (30)
Indeterminate	8 (2)	4 (1)	12 (2)
Time since initial diagnosis to first dose of study drug, months			
Median	42.2	44.2	42.8
Minimum, maximum	4, 306	3, 281	3, 306

Percentages are based on the total number of non-missing values reported for the corresponding parameter.

a Biclonal defined as the production of 2 distinct monoclonal proteins.

b One patient in each group whose myeloma was unable to be classified is not included in the source table.

c The central laboratory normal reference ranges are as follows: corrected calcium, 2.125–2.65 mmol/L (8.5-10.6 mg/dL); creatinine, 0.76-1.27 mg/dL; hemoglobin, females: 115-150 g/L and males: 125-170 g/L; and creatinine clearance, 100-130 mL/min/1.73 m^2. Creatinine clearance is calculated using the Cockcroft-Gault formula: C × [140–Age(years)] × Weight (kg)/[72 × serum creatinine (mg/dL)], where multiplication factor C=1 for males, and C=0.85 for females. Corrected calcium (mmol/L) is calculated using the following formula: serum calcium (mmol/L)+0.0246 × [40–serum albumin (g/L)].

Table 31. Summary of analysis populations (Study C16010)

Parameter	Placebo+LenDex	Ixazomib+LenDex	Total
Intent-to-treat (ITT) population[a]	362 (100)	360 (100)	722 (100)
Safety population[b]	360 (99)[e]	360 (100)[e]	720 (100)
Per Protocol (PP) population[c]	353 (98)	348 (97)	701 (97)
Response-Evaluable population[d]	345 (95)	345 (96)	690 (96)

a The ITT population was defined as all patients who were randomized.
b The Safety population was defined as all patients who receive at least 1 dose of any study drug.
c The PP population was defined as all ITT patients who did not violate the terms of the protocol in a way that would have affected the study outcome significantly, as determined by the medical monitor, who was blinded to study drug assignment;
d The Response-Evaluable population was defined as patients who received at least 1 dose of study drug, had measurable disease at baseline, and at least 1 postbaseline response assessment.
e Two placebo regimen patients who erroneously received ixazomib regimen kits at some cycles during treatment were excluded from the Safety population of the placebo regimen and included in Safety population of the ixazomib regimen. Two patients in the ixazomib regimen were never dosed with any study drug and were excluded from the ixazomib regimen Safety population.

Outcomes and estimation

Primary efficacy endpoint: Progression free survival

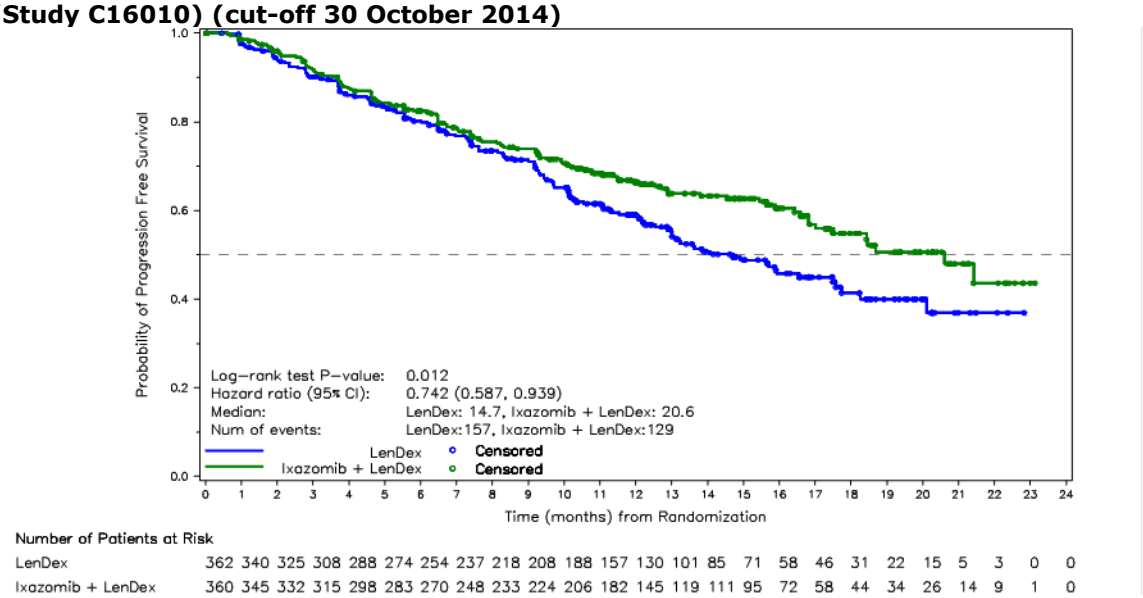
The outcome of the first interim analysis was reviewed by the IDMC on 5 February 2015 (data cut-off 30 October 2014 with 286 IRC-assessed events).

Table 32. Analysis of Progression Free Survival (PFS) Based on IRC assessment ITT Population (cut-off 30 October 2014)

	LenDex N = 362	Ixazomib + LenDex N = 360	Hazard Ratio (95% CI)[b] p-value[c]
Progression or Death (months)			0.742 (0.587, 0.939) 0.012
Number with Events (%)			
Progression	145 (40)	114 (32)	
Death	12 (3)	15 (4)	
Number Censored (%)	205 (57)	231 (64)	
25th Percentile (95% CI)	7.4 (6.18, 9.20)	8.2 (6.67, 10.12)	
Median (95% CI)	14.7 (12.91, 17.58)	20.6 (17.02, NE)	
75th Percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Min, Max	0.0*, 22.8*	0.0*, 23.1*	

NE = Not Estimable. NA: Kaplan Meier estimate not available due to no events in the interval. Censored observations are denoted by *. Only non-missing censoring categories are summarized in the table. a Based on Kaplan-Meier product limit estimates [n = number of subjects at risk]. b Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors: prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3) with treatment as a factor in the model. A less than 1 hazard ratio for treatment indicates better prevention of progression or death in Ixazomib + Lenalidomide and Dexamethosone arm as compared to Lenalidomide and Dexamethosone alone. c P-value tests the hypothesis of equal event times in both treatment arms obtained using the Log-rank test stratified by prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3).

Figure 7. Kaplan-Meier Plot of Progression-Free Survival Based on IRC Assessment (ITT) (Study C16010) (cut-off 30 October 2014)



Results were similar in a Cox regression analysis of PFS (HR=0.74; p=0.013).

The results of the updated analyses of PFS (data cut-off 12 July 2015) are presented in **Table 33** and **Figure 8.**

Table 33. Progression-Free Survival (IRC Assessments)—ITT Population (data cut-off 12 July 2015)

	Placebo+LenDex (N=362)	Ixazomib+LenDex (N=360)	Hazard Ratio
Progression or death (months)			
Number with events (%)			
Progression	180 (50)	158 (44)	
Death	15 (4)	19 (5)	
Number censored (%)	167 (46)	183 (51)	
25th Percentile (95% CI)	7.4 (6.18, 9.17)	8.2 (6.51, 9.92)	
Median (95% CI)	15.9 (13.21, 18.83)	20.0 (17.97, 23.43)	0.818 (0.67, 1.0)
75th Percentile (95% CI)	NE (NE, NE)	NE (28.81, NE)	
Minimum, maximum	0.0*, 30.9*	0.0*, 31.2*	
Kaplan-Meier survival probability estimate (95% CI)			
6 months	0.801 (0.754, 0.839) [n=262]	0.824 (0.779, 0.860) [n=272]	
9 months	0.708 (0.656, 0.753) [n=225]	0.732 (0.681, 0.776) [n=236]	
12 months	0.597 (0.541, 0.648) [n=186]	0.653 (0.599, 0.702) [n=203]	
18 months	0.463 (0.407, 0.518) [n=123]	0.554 (0.498, 0.607) [n=155]	
24 months	0.358 (0.298, 0.419) [n=43]	0.440 (0.380, 0.499) [n=61]	

Median follow-up, months (95% CI)	22.9 (21.78, 23.56)	23.3 (21.91, 23.79)
Reason for censoring, n (%)		
Alternate therapy	32 (9)	22 (6)
No baseline or no post-baseline assessment	5 (1)	6 (2)
Death or progression after >1 missed visit	9 (2)	8 (2)
Withdrawal of consent	6 (2)	7 (2)
Lost to follow-up	0	2 (<1)
No documented death or progression	115 (32)	138 (38)

* Censored observation.

Table 34. Progression-Free Survival (IRC Assessments)—EMA Censoring Rule, ITT Population (data cut-off 12 July 2015)

	Placebo+LenDex (N=362)	Ixazomib+LenDex (N=360)	Hazard Ratio
Progression or death (months)			0.822
Number with events (%)			
Progression	191 (53)	171 (48)	
Death	26 (7)	25 (7)	
Number censored (%)	145 (40)	164 (46)	
25th Percentile (95% CI)	7.2 (5.78, 8.28)	7.7 (6.47, 9.33)	
Median (95% CI)	15.0 (12.55, 17.58)	18.8 (16.59, 21.98)	
75th Percentile (95% CI)	NE (27.01, NE)	NE (27.86, NE)	
Minimum, maximum	0.0*, 30.9*	0.0*, 31.2*	
Kaplan-Meier survival probability estimate (95% CI)			
6 months	0.793 (0.747, 0.832) [n=275]	0.822 (0.777, 0.858) [n=281]	
9 months	0.686 (0.634, 0.731) [n=235]	0.725 (0.674, 0.769) [n=246]	
12 months	0.577 (0.523, 0.627) [n=194]	0.636 (0.582, 0.684) [n=210]	
18 months	0.436 (0.382, 0.488) [n=128]	0.528 (0.472, 0.580) [n=158]	
24 months	0.336 (0.280, 0.393) [n=44]	0.409 (0.351, 0.466) [n=62]	
Median follow-up (95% CI)—mo	22.9 (21.78, 23.56)	23.3 (21.91, 23.79)	
Reason for censoring—n (%)			
No baseline or no post-baseline assessment	5 (1)	6 (2)	
Withdrawal of consent	9 (2)	8 (2)	
Lost to follow-up	0	2 (<1)	
No documented death or progression	131 (36)	148 (41)	

Abbreviations: IRC=independent review committee, ITT=intent to treat, mo=month, NE=not estimable.
* Censored observation.

Figure 8. Kaplan-Meier Plot of Progression-Free Survival (IRC Assessments)—EMA Censoring Rule, ITT Population (data cut-off 12 July 2015)

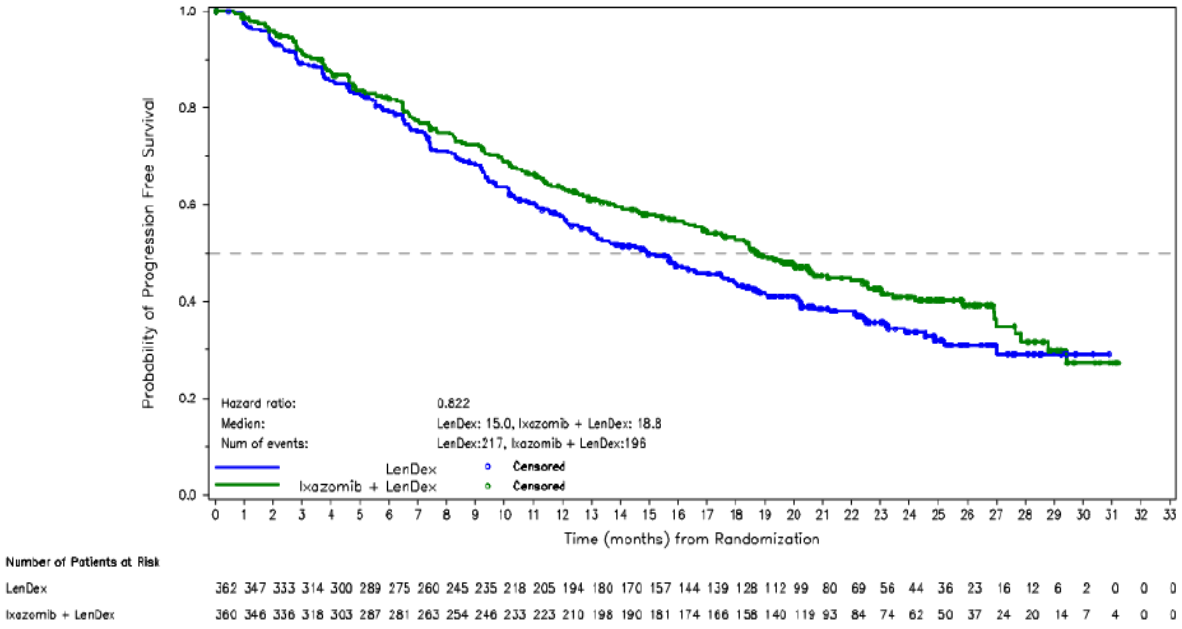
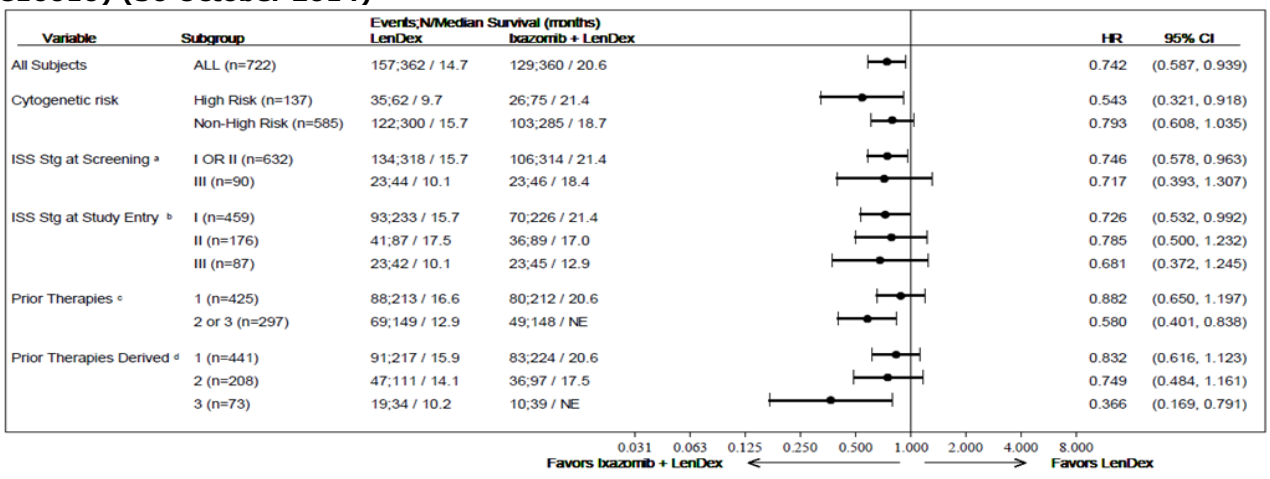
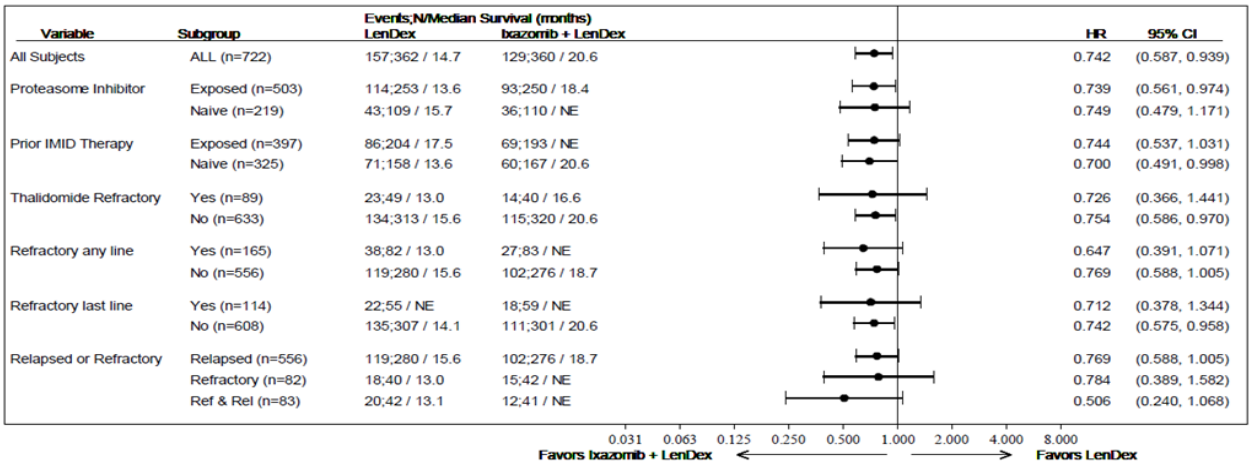
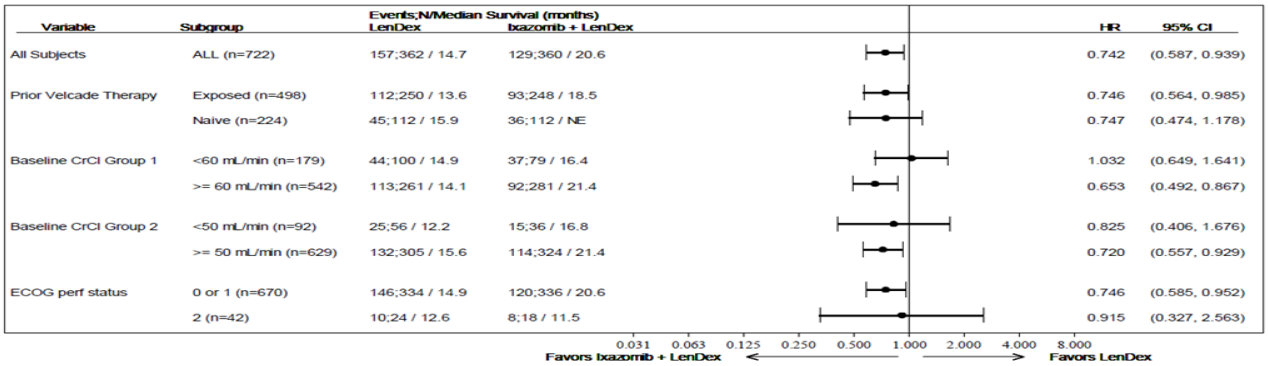


Figure 9. Forest Plot for Progression-Free Survival by Subgroup—ITT Population (Study C16010) (30 October 2014)







PFS was examined in patients with and without prior exposure to lenalidomide or thalidomide (**Table 35, Table 39).**

Table 35. Analysis of Progression Free Survival (PFS) Based on Prior Therapy of Lenalidomide ITT Population (Study C16010)

Lenalidomide Naïve	LenDex N = 318	Ixazomib + LenDex N = 316	Hazard Ratio (95% CI)[b] p-value[c]
Progression or Death (months)			0.766 (0.596, 0.985) 0.036
Number with Events (%)			
Progression	126 (40)	103 (33)	
Death	10 (3)	13 (4)	
Number Censored (%)	182 (57)	200 (63)	
25th Percentile (95% CI)	7.6 (6.47, 9.23)	8.1 (6.47, 10.12)	
Median (95% CI)	13.9 (12.55, 17.58)	20.6 (16.82, NE)	
75th Percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Min, Max	0.0*, 22.8*	0.0*, 23.1*	

Lenalidomide Exposed	LenDex N = 44	Ixazomib + LenDex N = 44	Hazard Ratio (95% CI)[b] p-value[c]
Progression or Death (months)			0.582 (0.275, 1.234) 0.153
Number with Events (%)			
Progression	19 (43)	11 (25)	
Death	2 (5)	2 (5)	
Number Censored (%)	23 (52)	31 (70)	
25th Percentile (95% CI)	5.2 (2.56, 10.32)	9.2 (1.87, NE)	
Median (95% CI)	17.5 (6.47, NE)	NE (15.67, NE)	
75th Percentile (95% CI)	20.1 (17.74, NE)	NE (NE, NE)	
Min, Max	1.0, 22.1*	0.6, 20.7*	

CI = Confidence interval; ISS = International Staging System; NA = Not Available (Kaplan Meier estimate not available due to no events in the interval); NE = Not Estimable.
Censored observations are denoted by *. Only non-missing censoring categories are summarized in the table.
a Based on Kaplan-Meier product limit estimates [n = number of subjects at risk].
b Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors: prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3) with treatment as a factor in the model. A less than 1 hazard ratio for treatment indicates better prevention of progression or death in Ixazomib + Lenalidomide and Dexamethosone arm as compared to Lenalidomide and Dexamethosone alone.
c P-value tests the hypothesis of equal event times in both treatment arms obtained using the Log-rank test stratified by prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3).

Table 36. Analysis of Progression Free Survival (PFS) Based on Prior Therapy of Thalidomide ITT Population (StudyC16010)

Thalidomide Naïve	LenDex N = 192	Ixazomib + LenDex N = 203	Hazard Ratio (95% CI)[b] p-value[c]
Progression or Death (months)			0.695 (0.505, 0.956) 0.024
Number with Events (%)			
Progression	82 (43)	63 (31)	
Death	6 (3)	9 (4)	
Number Censored (%)	104 (54)	131 (65)	
25th Percentile (95% CI)	7.4 (6.01, 9.23)	9.2 (7.00, 11.40)	
Median (95% CI)	13.6 (12.09, 16.56)	20.6 (16.82, NE)	
75th Percentile (95% CI)	NE (17.74, NE)	NE (21.42, NE)	
Min, Max	0.0*, 22.4*	0.0*, 22.8*	

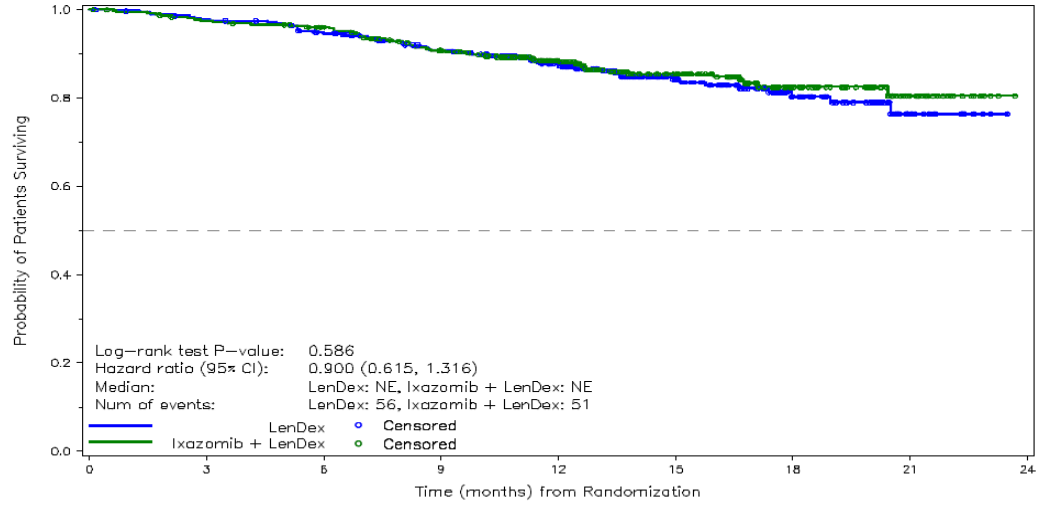
Thalidomide Exposed	LenDex N = 170	Ixazomib + LenDex N = 157	Hazard Ratio (95% CI)[b] p-value[c]
Progression or Death (months)			0.750 (0.523, 1.077) 0.118
Number with Events (%)			
Progression	63 (37)	51 (32)	
Death	6 (4)	6 (4)	
Number Censored (%)	101 (59)	100 (64)	
25th Percentile (95% CI)	7.4 (5.09, 9.69)	7.4 (4.86, 10.58)	
Median (95% CI)	15.7 (12.16, NE)	NE (16.43, NE)	
75th Percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Min, Max	0.0*, 22.8*	0.0*, 23.1*	

CI = Confidence interval; ISS = International Staging System; NA = Not Available (Kaplan Meier estimate not available due to no events in the interval); NE = Not Estimable.
Censored observations are denoted by *. Only non-missing censoring categories are summarized in the table.
a Based on Kaplan-Meier product limit estimates [n = number of subjects at risk].
b Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors: prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3) with treatment as a factor in the model. A less than 1 hazard ratio for treatment indicates better prevention of death in Ixazomib + Lenalidomide and Dexamethosone arm as compared to Lenalidomide and Dexamethosone alone.
c P-value tests the hypothesis of equal event times in both treatment arms obtained using the Log-rank test stratified by prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3).

Secondary endpoint: Overall survival

As of 30 October 2014, the 18-month survival rate was 83% in the ixazomib regimen and 80% in the placebo (**Figure 10**).

Figure 10. Kaplan-Meier Plot of Overall Survival—ITT Population (Study C16010) (cut-off 30 October 2014)



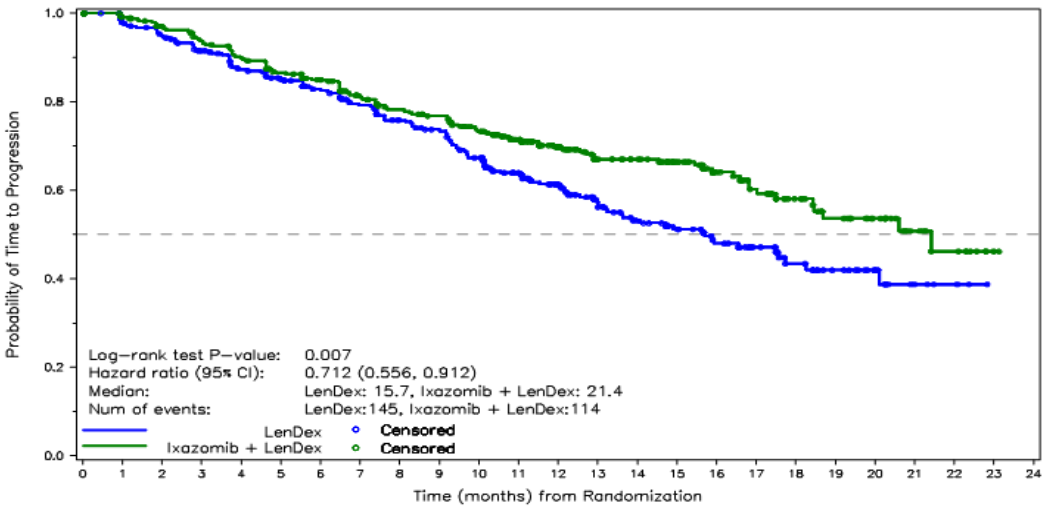
Number of Patients at Risk

LenDex	362	351	333	303	230	145	79	18	0
Ixazomib + LenDex	360	347	333	304	230	152	81	28	0

Secondary endpoint: Time to progression

The ixazomib regimen delayed the median time to disease progression by approximately 6 months (21.4 months vs 15.7 months; HR=0.712; CI 0.556, 0.912; p=0.007) (**Figure 11**).

Figure 11. Kaplan-Meier Plot of Time to Progression—ITT Population (Study C16010) (cut-off 30 October 2014)



Number of Patients at Risk

LenDex	362	338	324	306	285	271	254	237	218	208	187	157	129	100	85	71	58	46	31	22	15	5	3	0	0
Ixazomib + LenDex	360	342	328	313	298	281	269	248	232	223	205	182	145	118	111	95	72	58	44	34	26	14	9	1	0

Secondary endpoint: Overall Response Rate

Table 37. Response to Treatment Based on IRC Assessment—ITT Population (Study C16010) (cut-off 30 October 2014)

Confirmed Best Response	Placebo+LenDex N=362, n (%) [Exact 95% CI]	Ixazomib+LenDex N=360, n (%) [Exact 95% CI]	OR	[95% CI]	p-value
Overall response rate: CR+PR (including sCR and VGPR)	259 (71.5) [66.6, 76.1]	282 (78.3) [73.7, 82.5]	1.44	[1.03, 2.03]	0.035
CR+VGPR (including sCR)	141 (39.0) [33.9, 44.2]	173 (48.1) [42.8, 53.4]	1.45	[1.08, 1.95]	0.014
CR	24 (6.6) [4.3, 9.7]	42 (11.7) [8.5, 15.4]	1.87	[1.10, 3.16]	0.019
sCR	3 (<1) [0.2, 2.4]	9 (2.5) [1.1, 4.7]			
PR	235 (64.9) [59.8, 69.8]	240 (66.7) [61.5, 71.5]			
VGPR	117 (32.3) [27.5, 37.4]	131 (36.4) [31.4, 41.6]			
SD	59 (16.3) [12.6, 20.5]	40 (11.1) [8.1, 14.8]			
PD	20 (5.5) [3.4, 8.4]	17 (4.7) [2.8, 7.5]			

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; sCR=stringent complete response;
SD=stable disease; VGPR=very good partial response

Other secondary endpoints:

Among all patients, the median time to a response of PR or better was 1.1 month in the ixazomib regimen and 1.9 months in the placebo regimen (HR=1.242; p=0.009).

Median DOR was 20.5 months in ixazomib vs 15.0 months in placebo arm.

Secondary endpoint: Pain response

Among patients with a baseline worst pain score of ≥4 (n=356), 99 of 184 ixazomib regimen patients (54%) and 86 of 172 (50%) placebo regimen patients achieved a pain response (p=0.3909); the median time to pain response was shorter in ixazomib arm.

Table 38. Analysis of Time to Pain Response in Subjects with Baseline Worst Pain Score >=4 TT Population (Study C16010)

	LenDex N = 172	Ixazomib + LenDex N = 184	Hazard Ratio (95% CI)[b] p-value[c]
Time to Pain Response[a] (months)			1.147 (0.856, 1.536) 0.348
Number with Events (%)	86 (50)	99 (54)	
Number Censored (%)	86 (50)	85 (46)	
25th Percentile (95% CI)	1.9 (1.05, 2.04)	1.9 (1.22, 2.14)	
Median (95% CI)	6.0 (3.75, 16.89)	4.7 (2.92, 7.85)	
75th Percentile (95% CI)	NE (17.51, NE)	NE (NE, NE)	
Min, Max	0.0*, 22.9*	0.0*, 22.1*	

Censored observations are denoted by *. Only non-missing censoring categories are summarized in the table.
a Time to pain response is defined as the time from randomization to the first documented pain response.
b Hazard ratio is based on a stratified Cox's proportional hazard regression model with stratification factors: prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3) with treatment as
a factor in the model. A greater than 1 hazard ratio for treatment indicates better time to pain response in Ixazomib + Lenalidomide and Dexamethosone arm as compared to Lenalidomide and Dexamethosone alone.
c P-value tests the hypothesis of equal event times in both treatment arms obtained using the Log-rank test stratified
by prior therapies (1, 2 or 3), proteasome inhibitor (exposed, naïve), and ISS Stage at Screening (1 or 2, 3).
d Probability of being event-free based on Kaplan-Meier product limit estimates [n=number of subjects at risk]

<u>Exploratory endpoints</u>

Quality-of-Life Assessments

Global health scores on the EORTC QLQ-C30 over time were consistently similar in the 2 treatment regimens. There was a trend for better physical functioning, emotional functioning, and fatigue scores for the ixazomib regimen. Results of the MY-20 were also generally similar in the 2 treatment regimens, including the results of the subscale measuring side effects of treatment (**Figure12, Figure 15).**

Figure12.EORTC QLQ-C30 Global Health Status Score Over Time—ITT Population (Study C16010)

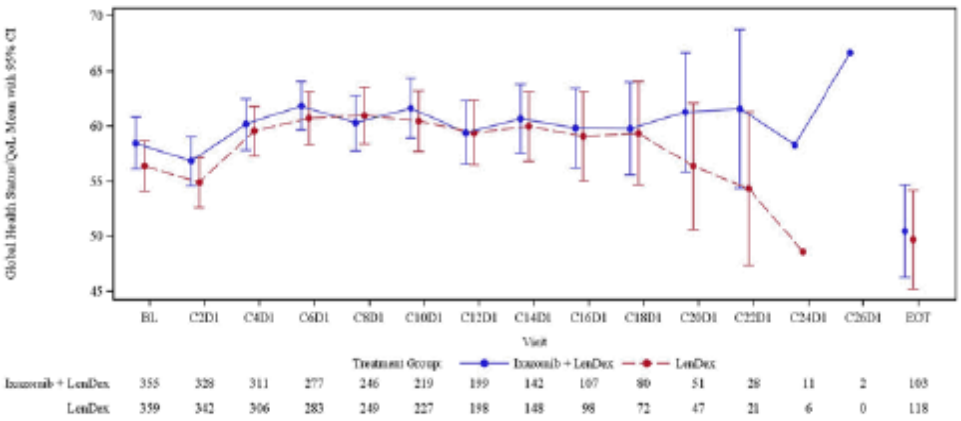
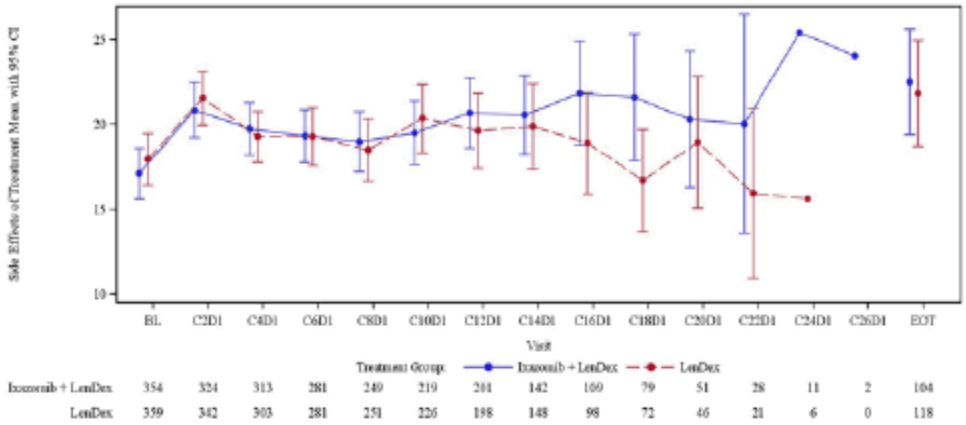


Figure 13. MY-20 Score for Side Effects of Treatment Over Time—ITT Population (Study C16010)



Ancillary analyses

Efficacy in patients with patients that had received prior stem cell transplant

Table 39. Response to Treatment, Progression-Free Survival, and Time to Progression by Number of Prior Lines of Therapy (Per Takeda Review) and Prior Stem Cell Transplant—ITT Population (cut-off 30 October 2014)

	N		ORR (%)		VGPR+CR (%)		CR or better (%)		Median PFS (months)			Median TTP (months)		
Prior Therapy	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**HR**	**P+Ld**	**I+Ld**	**HR**
All patients	**362**	**360**	**72**	**78**	**39**	**48**	**7**	**12**	**14.7**	**20.6**	**0.742**	**15.7**	**21.4**	**0.712**
No Prior SCT	163	148	68	78	35	51	5	12	12.2	18.5	0.540	12.9	NE	0.518
Any Prior SCT	199	212	74	79	42	46	8	11	18.3	20.6	0.988	20.1	21.4	0.943
Prior ASCT	193	202	74	80	42	47	8	11	18.3	20.6	0.915	18.3	21.4	0.876
Prior Allo-SCT or both Allo- and ASCT	6	10	100	50	33	30	17	10	NE	7.9	5.609	NE	7.9	5.609

Allo-SCT=allogeneic SCT; ASCT=autologous SCT; CR=complete response; I+Ld=ixazomib+LenDex; ITT=intent-to-treat; NE=not estimable; ORR=overall response rate; PFS=progression-free survival; P+Ld=placebo+LenDex; SCT=stem cell transplant, TTP=time to progression; VGPR=very good partial response.

Table 40. Response to Treatment, Progression-Free Survival, Time to Progression, and OS by Prior Stem Cell Transplant—ITT Population (12 July 2015)

	Number		ORR (%)		VGPR+ CR (%)		CR or better (%)		Median PFS (months)			Median TTP (months)			Overall Survival (months)		
Prior SCT	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**HR (p-value)**	**P+Ld**	**I+Ld**	**HR (p-value)**	**P+Ld**	**I+Ld**	**HR (p-value)**
No	163	148	69	78	40	53	9	16	12.9	20.5	0.674 (0.014)	13.2	23.0	0.649 (0.010)	NE	NE	0.743 (0.186)
Yes	199	212	76	79	47	50	12	14	18.8	19.6	0.977 (0.869)	20.2	21.2	0.951 (0.735)	NE	NE	1.032 (0.885)

I=ixazomib; LD=LenDex; NE=not estimable, P=placebo; SCT=stem-cell transplant.

Efficacy in patients with high risk cytogenetics

A total of 137 patients (75 ixazomib/62 placebo) had high-risk cytogenetic abnormalities and efficacy was assessed in the following subgroups:

- overall high-risk: patients with del(17), t(4;14), and t(14;16) combined
- del(17) positive (n=69): patients with del(17) alone (n=51) or in combination with either or both of the translocations t(4;14) and t(14;16) (n=18)
- t(4;14) translocation alone (n=61)
- t(14;16) translocation alone (n=7)A consistent treatment effect was observed across the high-risk subgroups for the ixazomib regimen and it was similar to the ixazomib effect seen in patients without high-risk cytogenetics.

A summary of response to treatment, PFS, and TTP for the overall study population, patients with high-risk cytogenetics, and patients without high-risk cytogenetics is presented in **Table 41** (cut-off 30 October 2014).

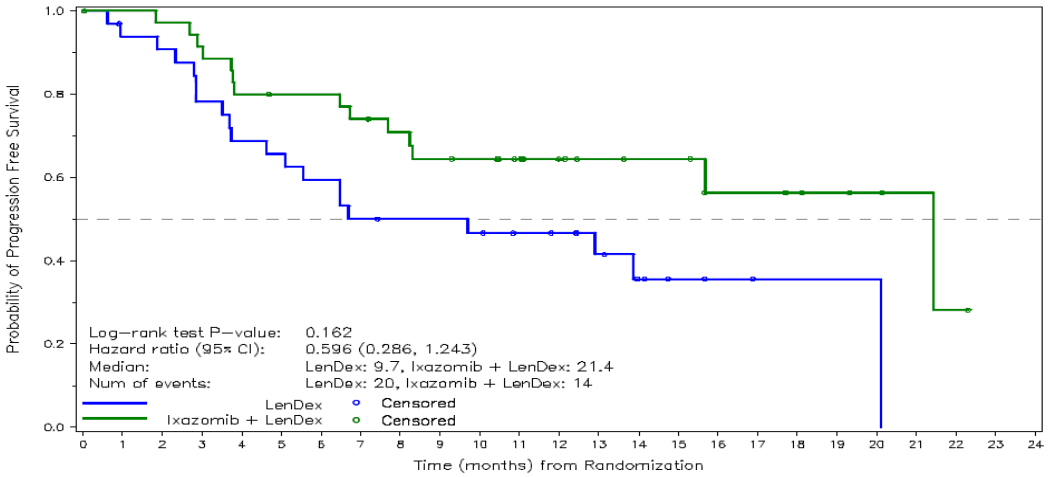
Table 41. Response to Treatment, PFS, and TTP for High-Risk Patients—ITT Population (Study C16010) (cut-off 30 October 2014)

	ORR (%)		**VGPR or better (%)**		**CR or better (%)**		**Median PFS (months)**			**Median TTP (months)**		
	P+Ld	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**P+Ld**	**I+Ld**	**HR**	**P+Ld**	**I+Ld**	**HR**
All patients	71.5	78.3[a]	39.0	48.1[a]	6.6	11.7[a]	14.7	20.6	0.742[a]	15.7	21.4	0.712[a]
Non-high-risk patients	74.0	78.2	42.7	48.8	7.7	11.6	15.7	18.7	0.793	17.5	NE	0.747
High-risk patients	59.7	78.7[a]	21.0	45.3[a]	1.6	12.0[a]	9.7	21.4	0.543[a]	12.0	21.4	0.534
Patients with del(17)	48.5	72.2	15.2	38.9	0	11.1[a]	9.7	21.4	0.596	--	--	--
Patients with t(4;14)	76.0	88.9	28.0	52.8	4.0	13.9	12.0	18.5	0.645	--	--	--

a p<0.05 for comparison between regimens

The Kaplan-Meier plot of PFS in high-risk patients harboring del(17) is displayed in **Figure 16.**

Figure 14. Kapan-Meier Plot of Progression-Free Survival in High-Risk Patients Harboring Del(17)—ITT Population(Study C16010) (cut-off 30 October 2014)

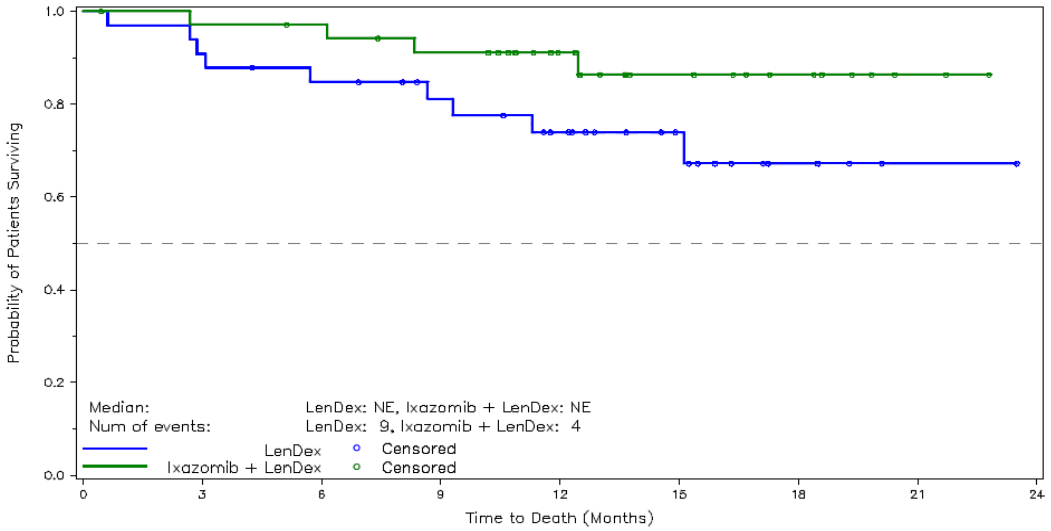


Number of Patients at Risk

LenDex	33	30	29	25	22	21	19	16	15	15	14	12	11	8	5	3	2	1	1	1	0	0	0	0
Ixazomib + LenDex	36	35	34	32	28	27	27	25	22	20	19	16	12	10	9	9	6	6	5	4	3	2	1	0	0

A total of 69 patients (36 ixazomib/33 placebo) had del(17) and as of 30 October 2014, 11% of ixazomib patients and 27% of placebo had died representing a 49% reduction in the risk of death for patients treated with ixazomib (HR=0.506) (**Figure 15**).

Figure 15. Kaplan-Meier Plot Overall Survival in High-Risk Patients Harboring Del(17) ITT (Study C16010) (cut-off 30 October 2014)



Number of Patients at Risk

LenDex	33	30	27	23	18	11	4	1	0
Ixazomib + LenDex	36	34	33	30	22	11	7	2	0

A summary of response to treatment, PFS, and TTP for the overall study population, patients with high-risk cytogenetics, and patients without high-risk cytogenetics is presented in **Table 42** (cut-off 12 July 2015).

Table 42. Overall Survival, Response to Treatment, Progression-Free Survival, and Time to Progression for High-Risk Patients—ITT Population (cut-off 12 July 2015)

Patients	ORR (%)		VGPR or better (%)		CR or better (%)		Median PFS (months)			Median TTP (months)			Median OS (months)		
	P+ Ld	I+Ld	P+ Ld	I+Ld	P+ Ld	I+Ld	P+ Ld	I+Ld	HR	P+ Ld	I+Ld	HR	P+ Ld	I+Ld	HR
All	73.2	78.6	43.9	51.4	10.2	14.7	15.9	20.0	0.818	17.6	22.4	0.792	NE	NE	0.868
Non-high-risk (a)	75.0	78.6	48.3	52.3	12.0	14.4	16.6	21.2	0.75	18.8	23.4	0.81	-	-	-
Standard risk	75	80	48	55	12	15	16.6	21.2	0.75	18.3	23.0	0.731	NE	NE	0.780
High-risk (b)	64.5	78.7	22.6	48.0	1.6	16.0	9.3	18.7	0.62	9.7	18.9	0.63	28.6	NE	0.576
With del(17) alone	54.5	72.2	18.2	41.7	0	13.9	9.7	15.7	0.82	11.8	15.7	0.83	30.9	NE	0.487
With t(4;14) alone	80.0	88.9	28.0	55.6	4.0	19.4	9.3	19.1	0.59	9.3	19.1	0.59	28.6	NE	0.456

CR=complete response; I+Ld=ixazomib+LenDex; ITT=intent-to-treat; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; P+Ld=placebo+LenDex; TTP=time to progression; VGPR=very good partial response.
(a) Non-high-risk patients included patients with standard risk and patients whose cytogenetic risk was unavailable.

(b) High-risk patients are defined as subjects carrying: del (17), translocation t(4;14) or t(14;16).

Efficacy in Adverse Risk Subpopulation (patients with either elevated-risk cytogenetic abnormalities [del(17), t(4;14), t(14;16), or 1q21+] or clinical adverse risk factors (ISS stage III) or patients previously treated with 2 or 3 prior therapies)

Table 43. Response to Treatment, Progression-Free Survival, Time to Progression, and Overall Survival— Adverse Risk Subpopulation (Primary Analysis and 12 July 2015 Analysis)

	N		ORR (%)		Median PFS (months)			Median TTP (months)			Median OS (months)		
	P+Ld	I+Ld	P+Ld	I+Ld	P+Ld	I+Ld	HR (p value)	P+Ld	I+Ld	HR (p value)	P+Ld	I+Ld	HR (p value)
Primary analysis	249	252	67	77	12.2	18.4	0.700 (0.009)	13.0	18.7	0.687 (0.009)	NE	NE	0.675 (0.075)
12 July 2015 analysis	249	252	69	77	12.9	18.9	0.745 (0.015)	13.9	20.0	0.733 (0.014)	30.9	NE	0.706 (0.047)

Figure16. Kaplan-Meier Plot of Progression-Free Survival— Adverse Risk Subpopulation (Primary Analysis)

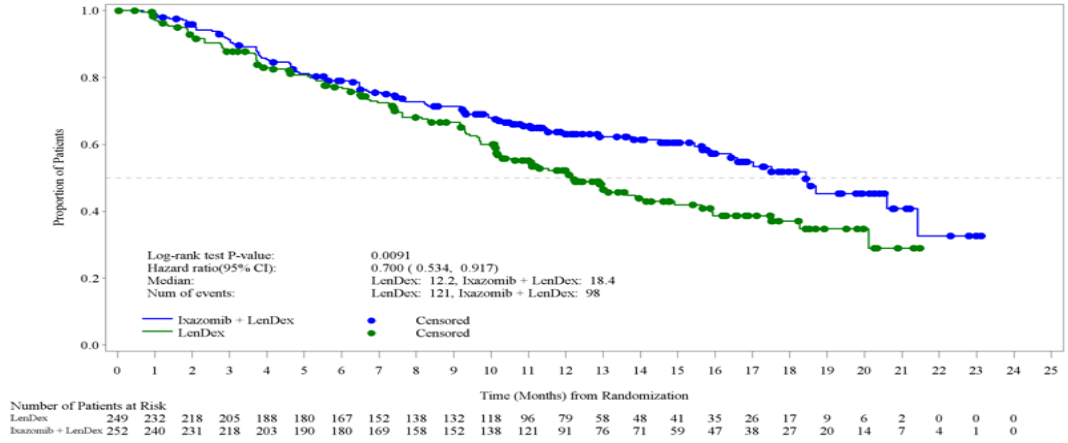
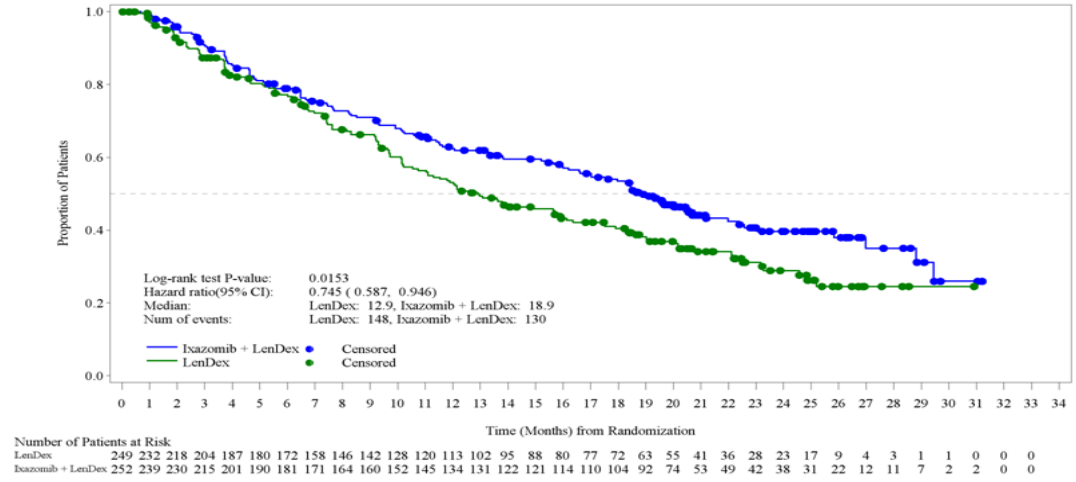


Figure 17. Kaplan-Meier Plot of Progression-Free Survival— Adverse Risk Subpopulation (cut-off 12 July 2015))



Efficacy in expanded high risk cytogenetics population (patients with del(17), t(4:14),t(14;16), and/or 1q21+)

Table 44. Response to Treatment, Progression-Free Survival, and Time to Progression, and Overall Survival—Expanded High-Risk Cytogenetics (Primary Analysis and cut-off 12 July 2015)

	ORR n (%)		Median PFS (months)			Median TTP (months)			Median OS (months)		
Patients	P+Ld n=154	I+Ld n=155	P+Ld n=154	I+Ld n=155	HR (p-val)	P+Ld n=154	I+Ld n=155	HR (p-val)	P+Ld n=154	I+Ld n=155	HR (p-val)
Primary Analysis											
Expanded high-risk	100 (65)	116 (75)	11.1 (83/154)	17.5 (62/155)	0.664 (0.016)	12.1 (77/154)	18.5 (58/155)	0.672 (0.024)	NE (33/154)	NE (19/155)	0.553 (0.040)
12 July 2015 Data Cutoff											
Expanded high-risk	105 (68)	116 (75)	11.3 (102/154)	18.0 (84/155)	0.702 (0.019)	12.3 (94/154)	18.4 (78/155)	0.725 (0.039)	28.6 (53/154)	NE (35/155)	0.620 (0.032)

Expanded high risk is defined as patients whose myeloma carries del(17), t(4;14), t(14;16),

and/or 1q21+.

Efficacy in expanded high risk cytogenetics plus patients with ISS stage III, refractory to any line, and/or those with 2-3 prior lines

Table 45. Overall Survival, Response to Treatment, Progression-Free Survival, and Time to Progression—Expanded High-Risk Cytogenetics, ISS Stage III, Refractory to Any Line, and/or 2-3 Prior Lines (Primary Analysis and cut-off 12 July 2015)

	ORR n (%)		Median PFS (months)			Median TTP (months)			Median OS (months)		
Patients	**P+Ld n=362**	**I+Ld n=360**	**P+Ld n=362**	**I+Ld n=360**	**HR (p-val)**	**P+Ld n=362**	**I+Ld n=360**	**HR (p-val)**	**P+Ld n=362**	**I+Ld n=360**	**HR (p-val)**
Expanded High-Risk Cytogenetics, ISS Stage III, Refractory to Any Line, and/or 2-3 Prior Lines											
Primary Analysis											
Yes	171/254 (67)	203/265 (77)	12.2 (122/254)	18.5 (101/265)	0.693 (0.007)	13.0 (112/254)	18.7 (91/265)	0.681 (0.007)	NE (49/254)	NE (37/265)	0.696 (0.096)
No	88/108 (81)	79/95 (83)	NE (35/108)	NE (28/95)	0.881 (0.617)	NE (33/108)	NE (23/95)	0.769 (0.331)	NE (7/108)	NE (14/95)	2.388 (0.053)
12 July 2015 Data Cutoff											
Yes	175/254 (69)	201/263 (76)	12.9 (150/254)	19.1 (133/263)	0.736 (0.011)	13.9 (139/254)	20.0 (120/263)	0.724 (0.010)	30.9 (76/254)	NE (59/263)	0.706 (0.046)
No	90/108 (83)	82/97 (85)	NE (45/108)	26.9 (44/97)	1.055 (0.803)	NE (41/108)	26.9 (38/97)	0.995 (0.983)	NE (14/108)	NE (22/97)	1.895 (0.057)

Expanded high-risk cytogenetics is defined as del(17), t(4;14), t(14;16), and/or 1q21+.

Region

Efficacy in Europe (around two thirds of total population) reported a positive effect favouring the ixazomib regimen for all efficacy measures consistent with the global ITT population; median PFS (19.3 months vs 13.9 months; HR=0.829).

Table 46. Response to Treatment, Progression-Free Survival, Time to Progression, and Overall Survival for Patients from Europe with High-Risk Cytogenetics— cut-off 12 July 2015

Patients	**ORR (%)**		**VGPR or better (%)**		**CR or better (%)**		**Median PFS (months)**			**Median TTP (months)**			**Median OS (months)**		
	P+ Ld N=236	**I+Ld N=247**	**P+ Ld N=236**	**I+Ld N=247**	**P+ Ld N=236**	**I+Ld N=247**	**P+ Ld N=236**	**I+Ld N=247**	**HR**	**P+ Ld N=236**	**I+Ld N=247**	**HR**	**P+ Ld N=236**	**I+Ld N=247**	**HR**
All	72	81	41	51	10	12	13.9	19.3	0.829	15.0	20.5	0.814	NE	NE	0.805
Standard risk	71	84	42	55	10	12	14.9	20.5	0.731	15.9	21.2	0.744	NE	NE	0.722
High-risk (a)	64	76	22	42	0	15	9.3	18.9	0.597	9.7	18.9	0.599	28.6	NE	0.513
With del(17)	56	73	19	40	0	13	9.7	18.0	0.689	11.8	19.5	0.650	20.5	NE	0.373
With t(4;14)	75	85	25	48	0	19	9.3	19.1	0.659	9.3	19.1	0.659	28.6	NE	0.417

Western Countries

Compared with the placebo, the ixazomib regimen showed superior activity over placebo in patients in Western countries (median PFS 26.9 months vs 17.7 months, HR 0.672) and non-Western countries (median PFS 18.7 months vs 14.9 months, HR 0.868) (data not shown).

Japan

As of 30 October 2014, 286 patients in the global ITT population had a PFS event but only 4 patients were from Japan. As of the 12 July 2015 cut-off, 86 new PFS events occurred in the global ITT population since 30 October 2014 and 15 events (17%) occurred in patients from Japan (7 patients ixazomib/ 8 patients placebo).

Median PFS in the ixazomib regimen was less than that in the placebo among patients in Japan (17.0 vs 18.7 months; HR=1.327). In the study population excluding patients from Japan ("non-Japan"), the median PFS in the ixazomib and placebo regimens was 20.0 months and 15.6 months, respectively (HR=0.809), similar to the overall results at the primary PFS analysis in the ITT population (median PFS in ixazomib and placebo regimens: 20.6 and 14.7 months, respectively; HR=0.742).

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 47. Summary of Efficacy for trial C16010

Title: Ixazomib in combination with Lenalidomide and Dexamethasone for the treatment of relapsed/refractory multiple myeloma			
Study identifier	C16010, 2011-005496-17		
Design	Randomized, double-blind, placebo controlled multicenter, prospective Phase 3 study in subject with relapsed/refractory MM who have received at least one prior therapy.		
Hypothesis	Superiority		
Treatments groups	Ixazomib arm		Ixazomib 4 mg PO once weekly on days 1,8 and 15 in addition to Lenalidomide 25 mg on days 1 through 21 and Dexamethasone 40 mg on days 1,8,15 and 22 of a 28-days cycle Allocated to intervention (n=360)
	Placebo arm		Placebo once weekly on days 1,8 and 15 in addition to Lenalidomide 25 mg on days 1 through 21 and Dexamethasone 40 mg on days 1,8,15 and 22 of a 28-days cycle Allocated to intervention (n=362)
Endpoints and definitions	Primary Endpoint	**PFS**	Time from the date of randomization to the date of first documentation of disease progression based on central laboratory results and international myeloma working group (IMWG) criteria or death to any cause
	Secondary endpoint	**OS**	Time from the date of randomization to the date of death
	Secondary endpoint	**OS del(17)**	Time from the date of randomization to the date of death in high-risk patients carrying del(17)

	Secondary endpoint	**CR and VGPR rate**	Defined in the response-evaluable population according to International Myeloma Working Group (IMWG) uniform response criteria
	Secondary endpoint	**ORR**	Proportion of subjects who achieved CR, VGPR or partial response (PR) relative to the response-evaluable population
	Secondary endpoint	**TTP**	Time from randomization to the date of first documented progression

Results and Analysis

Analysis description	**Interim Analysis for PFS: Primary Analysis**		
Analysis population and time point description	Intent To Treat (ITT) Population by Independent Review Committee assessment Clinical cut-off of 30 October 2014		
Descriptive statistics and estimate variability	Treatment group	Ixazomib + LenDex	Placebo + LenDex
	Number of subject	360	362
	Median PFS (IRC assessment, months)	20.6	14.7
	95% CI	[17.02, NE]	[12.25, 517.58]
	Median TTP (months)	21.4	15.7
	95% CI	[18.43, NE]	[13.21, 18.27]
	Median OS (months)	NE	NE
	95% CI	[NE, NE]	[NE, NE]
	ORR (%)	78.3	71.5
	95% CI	[73.7, 82.5]	[66.6, 76.1]
	Median PFS in patients with del (17) (months)	21.4	9.7
	95% CI	[8.25, NE]	[3.75, 20.11]
	CR (%)	11.7	6.6
	95% CI	[8.5, 15.4]	[4.3, 9.7]

Effect estimate per comparison	Primary endpoint: PFS	Comparison groups	Iza/LenDex vs placebo/LenDex
		hazard ratio	0.74
		95% CI	(0.59; 0.94)
		P-value	0.012
	Secondary endpoint: TTP	Comparison groups	Iza/LenDex vs placebo/LenDex
		hazard ratio	0.71
		95% CI	(0.55; 0.91)
		P-value	0.007
	Secondary endpoint: ORR	Comparison groups	Iza/LenDex vs placebo/LenDex
		odds ratio	1.44
		95% CI	(1.03; 2.03)
		P-value	0.035

	Secondary endpoint: OS	Comparison groups	Iza/LenDex vs placebo/LenDex
		hazard ratio	0.90
		95% CI	(0.61; 1.32)
		P-value	0.586
	Secondary endpoint: OS in patients with del(17)	Comparison groups	Iza/LenDex vs placebo/LenDex
		hazard ratio	0.59
		95% CI	(0.28, 1.24)
		P-value	0.162
	Secondary endpoint: CR	Comparison groups	Iza/LenDex vs placebo/LenDex
		odds ratio	1.87
		95% CI	(1.1, 3.16)
		P-value	0.019
Notes	Patients were stratified by: 1 versus 2 or 3 prior therapies; PI-exposed versus PI-naïve and ISS Stage at screening of I or II versus III.		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

Table 48. Clinical Studies in Special Populations

	Age in years		
Parameter	**65-74 (Older subjects number/ total number, [%])**	**75-84 (Older subjects number/ total number, [%])**	**≥85 (Older subjects number/ total number, [%])**
Controlled trials[a]	288/722 (40)	119/722 (16)	10/722 (1)
Non controlled trials[b]	48/120 (40)	12/120 (10)	1/120 (<1)

a Patients in the controlled trials category are from the ITT population of Study C16010.

b Patients in the non-controlled trials category are from the safety population of Studies C16003 and C16004 (60 patients each).

Supportive studies

Studies C16003, C16004 and C16005 (see section 2.5.1 ''Dose response studies'').

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of ixazomib in combination with lenalidomide and dexamethasone was based on a single phase 3 study C16010. The study is considered of adequate design, placebo controlled and with appropriate clinical endpoints for the target indication in MM (primary endpoint PFS and OS as key secondary).

The patient inclusion/exclusion criteria reflect the target population of MM patients that have received at least one prior therapy. Excluding patients that are refractory to lenalidomide or proteasome inhibitors is acceptable.

The design of the study follows previous CHMP Scientific Advice except for the planned interim analyses that was not recommended in an application with a single pivotal study. The significance level planned for the interim analysis ($p<0.0163$) is not sufficiently high to replicate the evidence level which would be seen from two trials positive at $p<0.05$.

Additional data from two phase 1 studies that administered single agent ixazomib in a more heavily pre-treated MM population have been presented to further support the efficacy of ixazomib in RRMM and for justification of dose selected.

Efficacy data and additional analyses

In the pivotal study the primary endpoint PFS was met at the first planned interim analysis and its effect was initially considered clinically significant in the context of the disease and current available therapies. A median increase of 6 months with ixazomib regimen versus control is significant (PFS median 20.6 m vs 14.7 m; HR 0.742 [0.587, 0.939], p= 0.012), especially when compared with other available therapies. All the pre-specified sensitivity analyses for the primary endpoint were considered adequate.

The favourable PFS result was supported by positive results for secondary endpoints, including subgroup analysis and results in patients with high risk cytogenetics at the first analysis.

However the updated efficacy data on second interim analysis (data cut off July 2015) showed a reduced difference in effect between arms in the overall ITT population for PFS, RRs and TTP compared to previous analysis. A hazard ratio for PFS of 0.818 (0.666, 1.004), p=0.054 for the updated analysis is far short of the evidence required in an application with a single pivotal trial. The worsening of results between the initially submitted analysis and the updated analysis is also a concern, and suggests the data may not yet have reached maturity, and could possibly worsen further with extended follow-up. It is clear that if this second analysis had been the primary analysis for PFS the study would have failed. When EMA censoring rules were used, the hazard ratio for the updated analysis was greater still at 0.822 (0.68, 1.0). These analyses represent the most recently information we have on PFS and have to be taken into consideration. A p-value of 0.054 clearly does not represent the level of evidence that would be expected from a single pivotal trial.

The OS data is still not mature and at the updated analysis the HR was 0.868 (0.064, 1.17).

Following PFS and OS, the next endpoint in the pre-specified testing hierarchy was OS in High-Risk Patients with del(17). Though technically this should not be looked at, as OS in the overall population is not positive with a hazard ratio of 0.487. A similar result was seen in the analysis of OS in all high risk subjects (subjects carrying: del(17), translocation t(4;14) or t(14;16)) HR=0.576 (0.289, 1.149, p=0.113). The result for PFS in high risk subjects was HR=0.625 (0.40, 0.98) and a p value =0.037 but it is noted for the previous analysis cut-off, that the result was HR 0.543 (0.321, 0.918, p=0.021). The benefit of ixazomib seems greater in this sub-group than in the overall population though there is still great uncertainty over the true effect on PFS and OS.

The better outcome in placebo arm in the Japan region is surprising and adds uncertainty to the outcome in the global population. It is noted that Japanese patients represented a younger population with most of them having the disease at earlier stages. In all, it suggests as if ixazomib exerts more activity in patients with poor prognosis. Regional effects may have contributed to the difference in PFS

between the first and second analysis, potentially because of some underlying differences in the patient populations. As compared to ITT population, Japan patients were younger (<65 years old: 59% vs 48%), more ISS stage I (78% vs 64%), more IMID naïve (78% vs 45%), and had more dose modifications during the study.

Time to next treatment data may have been helpful in further defining the real clinical benefit of treatment with ixazomib, however the data is still not mature.

An exploratory analysis in the subgroup of patients who received prior transplant was conducted and it is considered relevant in an early relapsed/refractory MM setting, when transplant is still an option. It is noted more than half of patients in the study had received prior SCT (199/362 in placebo and 212/360 in ixazomib arm), but the results in this subgroup of patients at the data cut-off October 2014 are of concern with a median PFS 20.6 months in the ixazomib arm versus 18.3 months in the placebo arm (HR 0.988) and provide uncertainty to the beneficial effect of adding ixazomib to lendex.

Analyses regarding prior transplant from the updated cut-off date of July 2015 in the ITT population, an approximate 7.6 month median PFS advantage (hazard ratio [HR]= 0.674; p=0.014) was observed with ixazomib in patients who had not received a prior SCT supported by data on TTP (HR 0.649, p=0.01) and ORR (78% vs 68% in the I+Ld and P+Ld groups respectively). However in subjects who received prior SCT, the observed clinical benefit in terms of median PFS (19.6 vs 18.8 months in the I+Ld and P+Ld groups respectively, HR=0.977), median TTP (HR 0.951) and ORR (~3%) is significantly reduced. A similar scenario is also observed with respect to the subpopulations with high risk cytogenetics.

There is lack of data on the feasibility of stem cell mobilization after exposure to ixazomib plus LenDex. Moreover, although it is reported that 4 patients discontinued ixazomib to receive stem cell transplant, no post-transplant outcome in patients treated with ixazomib was available.

The regional differences between western and non-western countries are notable and add further uncertainty especially in an application based on a single pivotal study.

Although no improvement in the quality of life, including pain response, was observed, the addition of ixazomib to the LenDex was not associated with a decrease in QoL scores. The latter observation is considered relevant, since tolerability is usually one of the main issues with triple-drug combinations in relapsed MM.

The data from China continuation study is difficult to interpret as the patient population were of a more advanced disease stage and unfortunately cytogenetics was not investigated. In all, it adds no significant support for this application.

Attempts were made to identify a higher-risk subgroup that may benefit from treatment with ixazomib.

The subgroup of patients called as the adverse risk subpopulation defined as the patients who received at least one prior therapy and have adverse risk characteristics, or who received at least two prior therapies reported a median PFS benefit of 6.2 months: 18.4 months in the ixazomib regimen versus 12.2 months in the placebo regimen at the primary analysis (HR= 0.700 [p=0.009]), and at the updated analysis a median PFS benefit of 6 months (18.9 months vs 12.9 months; HR=0.745 [p=0.015]). However the terminology of adverse risk characteristics is considered too broad and ambiguous and data in other subgroups with adverse risk characteristics (i.e. ECOG PS, >75 years of age, creatinine clearance < 60 ml/min etc) did not show benefit of ixazomib and raises concerns regarding the robustness of the decision based on with the risk of "cherry picking" in post-hoc analysis. In addition, restriction by prior lines of therapy may not be ideal in MM, due to the high heterogeneity of prior treatments.

Based on this, the applicant revised the indication to include adult patients with multiple myeloma who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+]; or experienced at least 2 relapses. However the CHMP concluded that the evidence of efficacy in the proposed indication is considered insufficient. The data are currently immature, especially for overall survival which is not yet evaluable. There is still the risk of "cherry picking" (i.e. the HR for PFS in del(17) patients was 0.596 in the primary analysis and 0.821 in the secondary analysis). Point estimates for efficacy measures are not sufficiently outstanding in the context of other available treatment options to compensate for the limitations of the available data. There is a lack of clinical rationale for post hoc arguments that efficacy is greater in the proposed population. The proposed high risk classification to identify eligible patients is not usually employed in clinical practice, and has not been validated in other studies.

There is substantial uncertainty associated with the interpretation of post hoc subgroup analyses, including a number of inconsistencies in the data regarding risk factors for early progression. Analyses in these subgroups were not statistically compelling and differences from the overall ITT population are considered likely to be chance findings. The changes between the analyses and the implications for data maturity (added to the general problems with post-hoc sub-group analyses) suggest that it is difficult to be confident in any positive sub-group results based on the current data-set.

2.5.4. Conclusions on the clinical efficacy

Efficacy of ixazomib in combination with lenalidomide and dexamethasone is not considered sufficiently demonstrated to support a positive benefit/risk balance in the proposed indication.

2.6. Clinical safety

Safety data have been collected in 1622 patients enrolled in ixazomib clinical trials.

For the purpose of this application discussions and comparisons are focused on data from two analyses:

- Pivotal placebo-controlled trial (C16010; N=720)
- Overall safety population (all patients who received at least 1 dose of oral ixazomib [either as a single agent or in combination with other agents, regardless of patient population] in 15 studies (Studies C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16010, C16011, C16013, C16015, C16017, C16018, C16020, and TB MC010034 [N=990]). Of note, it includes 360 patients from the pivotal study. The majority of patients had MM (80%), 51% of patients were enrolled in North America and 33% in Europe.

In addition, exposure data and an overall summary of AEs are also presented for all RRMM and NDMM patients who received at least 1 dose of oral ixazomib 4 mg on the weekly schedule +LenDex [Studies C16005 (phase 2 only), C16010, C16013, and TB MC010034 (combination agent cohort); N=460]).

Patient exposure

Extent of exposure

Table 49. Extent of Exposure (C16010 Safety Population, Ixazomib 4 mg (weekly) +LenDex, and Overall Safety Analysis Populations)

	Study C16010						Ixazomib 4 mg	Overall Safety
	Placebo+LenDex N=360			Ixazomib+LenDex N=360			(weekly)+LenDex Analysis Population[a] N=460	Analysis Population[b] N=990
	Placebo N=360	Len N=360	Dex N=359	Ixazomib N=360	Len N=359	Dex N=359	Ixazomib N=460	Ixazomib N=990
Overall treatment duration (days) of study drug								
Mean (std dev)	328.7 (171.35)	332.4 (171.66)	328.3 (171.93)	332.2 (179.57)	342.6 (178.75)	338.8 (177.28)	330.6 (205.39)	242.7 (237.40)
Median	334.0	337.0	335.0	340.5	350.0	346.0	323.0	174.5
Min, max	1, 696	2, 702	1, 703	1, 715	7, 718	1, 715	1, 1014	1, 1447
Number of treatment cycles[c]								
Mean (std dev)	12.0 (6.01)	12.0 (6.07)	11.9 (6.08)	12.0 (6.23)	12.2 (6.24)	12.2 (6.20)	12.0 (7.15)	9.2 (8.68)
Median	12.0	12.0	12.0	12.0	13.0	13.0	12.0	7.0
Min, max	1, 25	1, 25	1, 25	1, 26	1, 26	1, 26	1, 35	1, 69
Study drug dose intensity (%)[d]								n=989
Mean (std dev)	94.9 (10.23)	87.8 (21.59)	86.4 (18.93)	93.1 (10.47)	84.7 (22.03)	84.3 (18.64)	92.43 (11.042)	88.59 (17.545)
Median	98.2	95.6	95.0	97.4	93.8	92.8	96.84	96.19
Min, max	33, 100	10, 206	24, 175	33, 100	14, 204	25, 130	33.3, 100.0	24.7, 300.0

a Includes patients who received 4 mg dose of oral ixazomib+LenDex once weekly, from Studies C16005 (phase 2 only), C16010, C16013, and TB-MC010034 (4 mg ixazomib+LenDex combination cohort).

b Studies C16003, C16004, C16005, C16006, C16007, C16008, C16009, C16010, C16011, C16013, C16015, C16017, C16018, C16020, and TB-MC010034.

c A treatment cycle is defined as a cycle in which the patient received any amount of ixazomib or placebo, lenalidomide, or dexamethasone.

d Relative dose intensity is defined as: 100 * (Total amount of dose taken) / (Total prescribed dose of treated cycles), where total prescribed dose equals [dose prescribed at enrollment * number of prescribed doses per cycle * the number of treated cycles].

The pivotal study data showed the ixazomib arm was given over a median number of 12 cycles (max 26 = ~ 2 years), median relative dose intensity of ixazomib was high (97.4%) and the median relative dose intensity of lenalidomide and dexamethasone was similar in both arms. Ixazomib or placebo had the highest relative dose intensity and the lowest frequency of dose reductions. Up to 80% patients in the ixazomib arm did not have dose reduction, with 20% of patients having ≥1 ixazomib reduction and only 3% having 2 ixazomib reductions. The longest duration of exposure to ixazomib was reported in the overall safety analysis with 69 cycles (approximately 4 years).

Concomitant medications

Antithrombotic prophylaxis was required in studies including lenalidomide given the risk of thromboembolism. Other supportive care, eg, antiemetics, colony-stimulating factors, herpes zoster prophylaxis, and bisphosphonates were given at the physician's discretion.

In the pivotal study 97% patients received antithrombotic prophylaxis, the majority receiving aspirin (77%) and some patients were administered enoxaparin (24%) or nadroparin (9%) in a balanced manner in the two arms. Some differences between the ixazomib and placebo regimens, such as use of

antidiabetic medication (6% and 13%, respectively), were associated with baseline differences in medical history (eg, diabetes mellitus; 1 patient [<1%] and 7 patients [2%], respectively) rather than differences due to an effect of the treatment regimens themselves. A higher proportion of patients in the ixazomib regimen than placebo used antihistamines for systemic use (27% and 19%, respectively).

Adverse events

Table 50. Summary of Treatment-Emergent Adverse Events study C16010 (cut-off 12 July 2015)

	n (%)	
	Placebo+LenDex N=359	**Ixazomib+LenDex N=361**
Any TEAE	357 (99)	355 (98)
Grade 3 or higher TEAE	247 (69)	267 (74)
Drug regimen-related TEAE[a]	329 (92)	335 (93)
Drug regimen-related Grade 3 or higher TEAE (a)	190 (53)	218 (60)
SAE	177 (49)	168 (47)
Drug regimen-related SAE (a)	92 (26)	92 (25)
TEAE resulting in dose modification of 1 or more of the 3 agents in the study drug regimen (b)	250 (70)	271 (75)
TEAE resulting in dose reduction of 1 or more of the 3 agents in the study drug regimen	181 (50)	203 (56)
TEAE resulting in discontinuation of 1 or more of the 3 agents in the study drug regimen	73 (20)	91 (25)
TEAE resulting in discontinuation of the full study drug regimen	50 (14)	60 (17)
On-study death[c]	23 (6)	15 (4)

Abbreviations: SAE=serious adverse event; TEAE=treatment-emergent adverse event.
(a) TEAE assessed by the investigator as related to any drug in the drug combination (placebo, ixazomib, lenalidomide, or dexamethasone) was considered to be treatment related.
(b) Dose modification includes dose delay, dose reduction, and drug discontinuation, the latter which could represent discontinuation of an individual drug in the combination or a discontinuation of the full treatment regimen.
(c) On-study deaths are defined as deaths that occur within 30 days of the last dose of study drug.

Common AE

Table 51. Treatment-Emergent Adverse Events That Occurred in at Least 10% of Patients in Either the Ixazomib Regimen or Placebo Regimen by Preferred Term (C16010 Safety Population- data cut off 12 July 2015)

	n (%)									
	12 July 2015									
	Placebo+LenDex N=359					Ixazomib+LenDex N=361				
Preferred Term	**TEAE**	**Rel[a]**	**Gr ≥3**	**SAE**	**D/C**	**TEAE**	**Rel[a]**	**Gr ≥3**	**SAE**	**D/C**
Diarrhoea	139 (39)	75 (21)	9 (3)	2 (<1)	3 (<1)	164 (45)	110 (30)	23 (6)	9 (2)	6 (2)
Constipation	94 (26)	58 (16)	1 (<1)	1 (<1)		126 (35)	71 (20)	1 (<1)	1 (<1)	
Fatigue	102 (28)	67 (19)	10 (3)		3 (<1)	106 (29)	75 (21)	13 (4)		5 (1)
Neutropenia	92 (26)	83 (23)	71 (20)	2 (<1)	3 (<1)	103 (29)	93 (26)	74 (20)	2 (<1)	3 (<1)
Nausea	79 (22)	32 (9)			0	104 (29)	69 (19)			0
Anaemia	98 (27)	57 (16)	48 (13)	8 (2)	2 (<1)	103 (29)	60 (17)	34 (9)	3 (<1)	2 (<1)
Oedema peripheral	73 (20)	35 (10)	4 (1)	1 (<1)	0	101 (28)	47 (13)	8 (2)	1 (<1)	0
Back pain	62 (17)	1 (<1)	9 (3)	7 (2)		87 (24)	5 (1)	3 (<1)	2 (<1)	
Vomiting	42 (12)	15 (4)	2 (<1)		0	84 (23)	59 (16)	4 (1)		0
Thrombocytopenia	41 (11)	32 (9)	22 (6)	5 (1)	4 (1)	86 (24)	77 (21)	55 (15)	5 (1)	4 (1)
Nasopharyn gitis	73 (20)	5 (1)	0	0	0	81 (22)	8 (2)	0	0	0
Upper respiratory tract infection	70 (19)	15 (4)	3 (<1)	2 (<1)	0	83 (23)	14 (4)	2 (<1)	1 (<1)	0
Insomnia	98 (27)	75 (21)	11 (3)	0		73 (20)	54 (15)	7 (2)	0	
Peripheral sensory neuropathy	53 (15)	45 (13)	4 (1)	0	1 (<1)	69 (19)	56 (16)	6 (2)	0	7 (2)
Muscle spasms	95 (26)	68 (19)		0		66 (18)	42 (12)		0	
Asthenia	57 (16)	30 (8)	3 (<1)			58 (16)	33 (9)	8 (2)		
Bronchitis	51 (14)	13 (4)	7 (2)	8 (2)	0	60 (17)	15 (4)	1 (<1)	3 (<1)	0
Cough	57 (16)	9 (3)	0	0	0	58 (16)	4 (1)	0	0	0
Pyrexia	75 (21)	18 (5)	7 (2)	16 (4)	3 (<1)	56 (16)	15 (4)	4 (1)	12 (3)	1 (<1)
Dizziness	35 (10)	18 (5)	1 (<1)	0		49 (14)	23 (6)	2 (<1)	0	
Decreased appetite	38 (11)	15 (4)	4 (1)		2 (<1)	46 (13)	23 (6)	4 (1)		2 (<1)
Hypokalaemia	37 (10)	11 (3)	5 (1)	1 (<1)	0	47 (13)	10 (3)	16 (4)	1 (<1)	0
Arthralgia	39 (11)	1 (<1)	1 (<1)		0	45 (12)	3 (<1)	5 (1)		0
Headache	42 (12)	9 (3)	1 (<1)	0		44 (12)	12 (3)	1 (<1)	0	
Pain in extremity	31 (9)	4 (1)	2 (<1)		0	43 (12)	6 (2)	1 (<1)		0
Pneumonia	44 (12)	26 (7)	31 (9)	31 (9)	3 (<1)	41 (11)	22 (6)	29 (8)	26 (7)	1 (<1)
Dyspnoea	40 (11)	10 (3)	5 (1)	4 (1)		40 (11)	10 (3)	2 (<1)	2 (<1)	
Pruritus	25 (7)	19 (5)		0	0	38 (11)	21 (6)		0	0
Tremor	37 (10)	24 (7)		0	0	21 (6)	11 (3)		0	0
Cataract	37 (10)	20 (6)	14 (4)			28 (8)	17 (5)	11 (3)		

Note: Shaded cells denote data removed to protect the scientific integrity of this ongoing blinded trial.

Abbreviations: D/C=adverse events resulting in discontinuation of 1 or more of the 3 agents in the study drug regimen; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

(a) TEAE assessed by the investigator as related to any drug in the drug combination (placebo, ixazomib, lenalidomide, or dexamethasone) was considered to be treatment related.

AEs of any grade (regardless of causality) with a difference of at least 5% between the ixazomib and placebo arms included diarrhoea, constipation, nausea, peripheral oedema, vomiting, thrombocytopenia, and maculopapular rash (more frequent with ixazomib arm), as well as insomnia, muscle spasm, and pyrexia(more frequent with placebo arm). Other AE that appear to have at least 5% difference between the two arms of pivotal study were due to rounding of events. Maculopapular rash was reported by 9% patients in ixazomib arm (vs 4% placebo) in the pivotal study.

In the pivotal study 20% of patients in ixazomib arm had at least one dose reduction of ixazomib but only 3% had 2 ixazomib reductions. The primary causes of dose reductions of ixazomib were thrombocytopenia, peripheral neuropathy, rash and neutropenia. Dose reduction of lenalidomide was more frequent in ixazomib arm (38% vs 28%) than placebo mainly due to thrombocytopenia, diarrhoea, renal failure, rash and neutropaenia. Similar frequency of dexamethasone dose reduction was seen in ixazomib and placebo arms (31% vs 27%), mainly due to insomnia, mood altered, peripheral oedema and diarrhoea.

AE Grade 3 or 4

Grade 3 AE occurred in 49% of patients in the ixazomib arm and 43% of patients in the placebo (C16010). Grade 3 TEAEs reported by ≥5% of patients in either the ixazomib or placebo regardless of causality were neutropenia (15% and 12%, respectively), anaemia (9% and 13%), thrombocytopenia (8% and 3%), diarrhoea (6% and 2%), and pneumonia (6% and 7%). The only Grade 3 with a regimen difference ≥5 % was thrombocytopenia.

Table 52. Grade 3 TEAE That Occurred in at Least 5 Patients in Either the Ixazomib Regimen or Placebo Regimen-C16010 Safety Population – data cut off 12 July 2015

	n (%)	
Preferred Term[a]	**Placebo+LenDex N=359**	**Ixazomib+LenDex N=361**
Patients with at least 1 Grade 3 TEAE	170 (47)	187 (52)
Neutropenia	53 (15)	60 (17)
Anaemia	48 (13)	34 (9)
Thrombocytopenia	13 (4)	34 (9)
Pneumonia	26 (7)	26 (7)
Diarrhoea	9 (3)	23 (6)
Leukopenia	3 (<1)	14 (4)
Fatigue	10 (3)	13 (4)
Cataract	14 (4)	11 (3)
Hypertension	4 (1)	11 (3)
Platelet count decreased	6 (2)	10 (3)
Hypokalaemia	4 (1)	9 (2)
Syncope[b]	8 (2)	9 (2)
Asthenia	3 (<1)	8 (2)
Muscular weakness	4 (1)	8 (2)
Neutrophil count decreased	13 (4)	8 (2)
Oedema peripheral	4 (1)	8 (2)
Bronchopneumonia	3 (<1)	7 (2)
Insomnia	11 (3)	7 (2)
Rash maculo-papular	3 (<1)	7 (2)
Atrial fibrillation	3 (<1)	6 (2)
Nausea		
Peripheral sensory neuropathy	4 (1)	6 (2)
Pulmonary embolism	8 (2)	6 (2)
Arthralgia	1 (<1)	5 (1)

Preferred Term[a]	n (%) Placebo+LenDex N=359	Ixazomib+LenDex N=361
Cardiac failure	4 (1)	5 (1)
Dyspnoea	5 (1)	2 (<1)
Febrile neutropenia	5 (1)	2 (<1)
Hyperglycaemia	7 (2)	5 (1)
Hypocalcaemia	5 (1)	4 (1)
Infection	2 (<1)	5 (1)
Influenza	3 (<1)	5 (1)
Lymphocyte count decreased	6 (2)	5 (1)
Mood altered	1 (<1)	5 (1)
Pyrexia	7 (2)	4 (1)
Respiratory tract infection	5 (1)	4 (1)
Back pain	9 (3)	3 (<1)
Hyponatraemia	6 (2)	3 (<1)
Urinary tract infection	6 (2)	3 (<1)
Renal failure acute	8 (2)	2 (<1)
Bronchitis	7 (2)	1 (<1)
Diabetes mellitus	8 (2)	1 (<1)
Renal failure chronic		

Note: Shaded cells denote data removed to protect the scientific integrity of this ongoing blinded trial.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; TEAE=treatment-emergent adverse event

a A patient reporting the same event more than once had that event counted only once within each preferred term using the highest intensity.

b Per CTCAE Version 4.03, syncope has only 1 grade, which is Grade 3.

Grade 4 AE occurred in 15% of patients in the ixazomib regimen and 14% of patients in the placebo. No Grade 4 AE had a regimen difference ≥5%. Grade 4 TEAEs experienced by >1% in either the ixazomib or placebo regimen were thrombocytopenia (6% and 2%, respectively), neutropenia (4% each), and hypokalaemia (2% and <1%).

The incidence in the overall safety analysis population of Grade 3 or 4 TEAEs was similar to that of the ixazomib regimen in C16010.

Adverse Reactions

Table 53. Adverse reactions in patients treated with NINLARO in combination with lenalidomide and dexamethasone (all grades, grade 3 and grade 4) in the pivotal clinical trial

	LenDex N=360 n (%)			Ixazomib + LenDex N=360 n (%)			Total N=720 n (%)	
Adverse Drug Reaction	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4	All Grade	Grade 3
Subjects with at Least 1 Adverse Drug Reaction	282 (78)	44 (12)	11 (3)	310 (86)	79 (22)	25 (7)	592 (82)	123 (17)
Back pain	57 (16)	9 (3)	0	74 (21)	2 (< 1)	0	131 (18)	11 (2)
Constipation	90 (25)	1 (< 1)	0	122 (34)	1 (< 1)	0	212 (29)	2 (< 1)
Diarrhoea	130 (36)	8 (2)	0	151 (42)	22 (6)	0	281 (39)	30 (4)
Nausea	74 (21)			92 (26)			166 (23)	6 (< 1)
Oedema peripheral	66 (18)	4 (1)	0	91 (25)	8 (2)	0	157 (22)	12 (2)
Peripheral neuropathies**	77 (21)	7 (2)	0	100 (28)	7 (2)	0	177 (25)	14 (2)
Rash***	38 (11)	5 (1)	0	68 (19)	9 (3)	0	106 (15)	14 (2)
Thrombocyto-penia*	50 (14)	16 (4)	11 (3)	99 (28)	37 (10)	25 (7)	149 (21)	53 (7)
Upper respiratory tract infection	52 (14)	2 (< 1)	0	69 (19)	1 (< 1)	0	121 (17)	3 (< 1)
Vomiting	38 (11)	2 (< 1)	0	79 (22)	4 (1)	0	117 (16)	6 (< 1)

Note: Shaded cells denote data removed to protect the scientific integrity of this ongoing blinded trial.

Other AE of significance

Thromboembolism

In C16010, 96% of the ixazomib and 98% of the placebo received thromboprophylaxis as per protocol. The addition of ixazomib to LenDex did not increase the risk of venous thromboembolism (ixazomib and placebo regimens of 7% vs 10%, respectively).

Herpes zoster

Antiviral prophylaxis was allowed at the physician's discretion. Herpes zoster reports were low (4% ixazomib regimen vs 2% placebo). In 3 patients (2 ixazomib, 1 placebo) were of Grade 3 and no patient had a Grade 4. The incidence among patients taking antiviral prophylactically was lower (0.4% each arm) than among the 236 patients (both arms) not taking prophylaxis with 18 (8%) reporting herpes zoster (13 of 113 patients (12%) in the ixazomib regimen vs 5 of 123 patients (4%) in the placebo).

New primary malignancies

No safety concern has been identified with regards to new primary malignancies in Study C16010 or the overall safety analysis population. The incidence was low, the same between the overall safety

analysis population and the ixazomib regimen in Study C16010 (2%) and consistent with the reported incidence in patients with RRMM treated with lenalidomide/dexamethasone.

Cardiac

In study C16010 the incidence of heart failure was 4% in the ixazomib regimen vs 5% in placebo and the incidence of myocardial infarction was 1% and 2% respectively. The incidence of cardiac arrhythmias was 16% in the ixazomib regimen vs 15% in placebo . No patient in the clinical program experienced Torsade de pointes. Most of the arrhythmias were of low grade.

Rash

Rash occurred in 36% of patients in the NINLARO regimen compared to 23% of patients in the placebo regimen. The most common type of rash reported in both regimens was maculo papular and macular rash. Grade 3 rash was reported in 3% of patients in the NINLARO regimen compared to 1% of patients in the placebo regimen. Rash resulted in discontinuation of one or more of the three medicinal products in < 1% of patients in both regimens.

The incidence of Rash (pooled PT) was highest during the first 3 months and generally declined over time.

A higher proportion of patients in the ixazomib regimen used antihistamines (15% vs 9%) or corticosteroids (5% vs 3%) for systemic use for a rash event.

In the overall safety analysis population, the incidence of rash reported as SAE was <1% (9 patients), including 2 patients (<1%) with Stevens-Johnson syndrome (1 of which codes to bullous erythema multiforme according to the current MedDRA version 18.0) and 1 patient (<1%) each with maculopapular rash, macular rash, rash generalized, rash morbilliform, erythema multiforme, acute febrile neutrophilic dermatosis, and interstitial granulomatous dermatitis. Overall, 6 patients (<1%) discontinued treatment due to macula-papular rash (2), Stevens-Johnson syndrome (1), acute febrile neutrophilic dermatosis (1), popular rash (1) and pruritic rash (1).

Gastrointestinal toxicity

Although there was a higher frequency in the ixazomib regimen than in the placebo of nausea (26% vs 21%) and vomiting (22% vs 11%) in Study C16010, nausea or vomiting did not result in drug discontinuation.

A higher incidence of diarrhoea was noted in the ixazomib regimen than in the placebo regimen (42% and 36%, respectively) in Study C16010.

Diarrhoea resulted in discontinuation of one or more of the three medicinal products in 1% of patients in the ninlaro regimen and < 1% of patients in the placebo regimen.

Thrombocytopaenia

In Study C16010, three percent of patients in the ixazomib regimen and 1% of patients in the placebo regimen had a platelet count $\leq$ 10,000/mm^3 during treatment. Less than 1% of patients in both regimens had a platelet count $\leq$ 5000/mm^3 during treatment. Thrombocytopenia resulted in discontinuation of one or more of the three drugs in < 1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Thrombocytopenia did not result in an increase in haemorrhagic events or platelet transfusions.

Peripheral neuropathy

Peripheral neuropathy occurred in 28% of patients in the ixazomib regimen compared to 21% of patients in the placebo regimen. Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (< 1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens.

Other

The overall safety analysis have reported infrequent incidences of tumor lysis syndrome (<1%), 1 report of SAE of transverse myelitis with ixazomib not well characterised, and 1 report of SAE of thrombotic thrombocytopenic purpura (oral ixazomib 5.5 mg) with recovery.

Long-term AE

In the ixazomib regimen of the pivotal study, the incidence of most categories of TEAEs declined with continued exposure, except for TEAEs leading to drug discontinuation of at least 1 of the 3 drugs which occurred most frequently in Cycles 13-18. Similar patterns were noted in the placebo regimen and indicate that the ixazomib regimen was tolerated with prolonged treatment. A similar profile of decreased incidence of AE over time was observed for the overall safety population.

Serious adverse event/deaths/other significant events

Serious adverse event

In Study C16010, SAEs occurred in 40% of patients in the ixazomib regimen and 44% of patients in the placebo. The most common SAE was pneumonia (6% ixazomib vs 8% placebo). There were no SAEs or SAEs related to study drug with a difference ≥5 % between the two regimens. Also the most common drug related SAEs was pneumonia (3% ixazomib vs 5% placebo). The incidence was similar in the overall safety analysis population. A summary of SAE is shown in **Table 54**.

Table 54. Serious TEAEs That Occurred in at Least 1% of Patients in the Overall Safety Analysis Population or in Either the Ixazomib or Placebo Regimen in Study C16010

	Study C16010		Overall Safety
Preferred Term	**Placebo+LenDex N=360**	**Ixazomib+LenDex N=360**	**Analysis Population N=990**
Patients with at Least 1 SAE[b]	158 (44)	143 (40)	403 (41)
Pneumonia	27 (8)	20 (6)	49 (5)
Pyrexia	14 (4)	10 (3)	27 (3)
Diarrhoea	2 (<1)	7 (2)	23 (2)
Dehydration	0	0	19 (2)
Renal failure acute	4 (1)	5 (1)	18 (2)
Vomiting			15 (2)
Thrombocytopenia	5 (1)	4 (1)	14 (1)
Atrial fibrillation	6 (2)	5 (1)	13 (1)
Back pain	6 (2)	1 (<1)	13 (1)
Hypotension			12 (1)

	Study C16010		Overall Safety
Preferred Term	**Placebo+LenDex N=360**	**Ixazomib+LenDex N=360**	**Analysis Population N=990**
Nausea			11 (1)
Pulmonary embolism	8 (2)	6 (2)	9 (<1)
Syncope	2 (<1)	4 (1)	9 (<1)
Plasma cell myeloma	8 (2)	5 (1)	8 (<1)
Plasmacytoma			8 (<1)
Deep vein thrombosis	5 (1)	4 (1)	7 (<1)
Influenza	2 (<1)	5 (1)	7 (<1)
Sepsis	4 (1)	3 (<1)	7 (<1)
Anaemia	8 (2)	3 (<1)	6 (<1)
Cardiac failure	4 (1)	2 (<1)	6 (<1)
Lung infection	4 (1)	2 (<1)	6 (<1)
Pathological fracture	1 (<1)	4 (1)	5 (<1)
Septic shock	5 (1)	2 (<1)	5 (<1)
Bronchopneumonia	2 (<1)	4 (1)	4 (<1)
Bronchitis	7 (2)	1 (<1)	3 (<1)
Febrile neutropenia	7 (2)	2 (<1)	3 (<1)
Lower respiratory tract infection	4 (1)	3 (<1)	3 (<1)
Urinary tract infection			3 (<1)
Spinal compression fracture	5 (1)	1 (<1)	1 (<1)

Note: Shaded cells denote data removed to protect the scientific integrity of this ongoing blinded trial.

Deaths

A total of 29 on-study deaths (within 30 days of the last dose of study drug) were reported in Study C16010 (database lock on 30 October 2014); 12 (3%) in the ixazomib regimen and 17 (5%) in the placebo. Deaths were more frequently documented in early cycles of therapy although some occurred up to cycle 21.

Over one-fourth (8/29; 28%) of on-study deaths were attributed to disease progression.

Twelve deaths (6 in each arm) were associated with cardiovascular events, 5 with infections (2 ixazomib / 3 placebo) and 4 were associated with other organ failure.

Five of 29 deaths were related to study drug treatment; 3 in the ixazomib regimen (pulmonary embolism, fungal pneumonia, and coma with concurrent stroke) and 2 in the placebo (myocardial infarction and pulmonary embolism).

The incidence of on-study deaths in the overall safety analysis population (4% /41 patients) was similar to that of the ixazomib regimen in C16010, also decreased over time and most (18 deaths or 44%) were due to progressive disease. Five of 41 deaths (3 in ixazomib regimen) were considered related to the study drug regimen (respiratory syncytial viral pneumonia, cardiorespiratory arrest, coma with concurrent stroke, pulmonary embolism, and fungal pneumonia). There were 30 (3%) deaths within 90 days of the first dose of study drug and the most common cause was plasma cell myeloma (6 patients).

Laboratory findings

Haematology

The percentage of patients in the pivotal study with a Grade 0, 1, or 2 haemoglobin or neutrophil value at baseline who shifted to a worst value of Grade 3 or 4 was similar between the ixazomib and placebo arms. A difference was noted for platelet count with a higher incidence of grade 3 and 4 thrombocytopaenia in the ixazomib arm. The data from the overall safety population is similar to the ixazomib regimen in the pivotal study.

Table 55. Patients with Select Grade 0, 1, or 2 Hematology Values at Baseline With Shift to Grade 3 or 4 Abnormalities as Worst Value on Study (C16010 Safety Population and Overall Safety Analysis Population)

Parameter	Shifted to Grade 3 n/N (%)	Shifted to Grade 4 n/N (%)
Hemoglobin (shift to low)		
Study C16010		
Placebo+LenDex	44/350 (13)	0/350
Ixazomib+LenDex	40/349 (11)	0/349
Overall Safety Analysis Population	74/717 (10)	6/717 (1)
Platelets (shift to low)		
Study C16010		
Placebo+LenDex	21/353 (6)	13/353 (4)
Ixazomib+LenDex	50/358 (14)	39/358 (11)
Overall Safety Analysis Population	100/732 (14)	76/732 (10)
Neutrophils (shift to low)		
Study C16010		
Placebo+LenDex	70/338 (21)	23/338 (7)
Ixazomib+LenDex	59/328 (18)	14/328 (4)
Overall Safety Analysis Population	101/628 (16)	25/628 (4)

Liver

Hepatotoxicity has been reported with the use of lenalidomide. Four patients out of whom 2 were from the pivotal study (1 ixazomib, 1 placebo) met the biochemical criteria for potential Hy's law.

In Study C16010, mean changes in liver function parameters were for the majority generally small and similar between arms. TEAE associated with liver impairment between ixazomib and placebo were 6% vs 5% respectively with shifts to grade 3 or 4 $\leq$ 1% in both arms.

Data from overall safety analysis population was similar to that reported for the ixazomib arm in the pivotal study.

Renal

There were no safety concerns with respect to renal impairment in the pivotal study, with a similar incidence in ixazomib and placebo arms (8% vs 10%), and shifts to grade 3 or 4 creatinine values below 2% in both arms.

Data from overall safety analysis population was similar to that reported for the izxazomib arm in the pivotal study.

Safety in special populations

Age

In the pivotal study the incidence of SAEs and on study death was similar across age groups. The incidence of Grade 3 or higher TEAEs, and TEAEs, in particular thrombocytopaenia, resulting in study drug regimen dose modification, dose reduction, or discontinuation tended to increase with baseline age but was observed for both regimens. No particular safety concerns were observed for the small group of 10 patients ≥ 85 years.

Table 56. C16010 Treatment-Emergent AE by Age (Safety Population)

	Placebo+LenDex N=360			**Ixazomib+LenDex N=360**		
	≤65 years N=174	**>65 and ≤75 years N=125**	**>75 years N=61**	**≤65 years N=169**	**>65 and ≤75 years N=144**	**>75 years N=47**
Any TEAE	172 (99)	123 (98)	60 (98)	160 (95)	144 (100)	47 (100)
Grade 3 or higher TEAE	101 (58)	81 (65)	39 (64)	104 (62)	103 (72)	36 (77)
Treatment-related TEAE	150 (86)	115 (92)	52 (85)	147 (87)	136 (94)	46 (98)
Treatment-related Grade 3 or higher TEAE[c]	72 (41)	68 (54)	27 (44)	86 (51)	80 (56)	30 (64)
SAE	63 (36)	62 (50)	33 (54)	63 (37)	61 (42)	19 (40)
Treatment-related SAE[c]	34 (20)	34 (27)	15 (25)	37 (22)	36 (25)	10 (21)
TEAE resulting in dose modification of 1 or more of the 3 agents in the study drug regimen	103 (59)	81 (65)	45 (74)	110 (65)	106 (74)	38 (81)
TEAE resulting in dose reduction of 1 or more of the 3 agents in the study drug regimen	68 (39)	60 (48)	32 (52)	77 (46)	82 (57)	27 (57)
TEAE resulting in discontinuation of 1 or more of the 3 agents in the study drug regimen	24 (14)	22 (18)	16 (26)	28 (17)	25 (17)	17 (36)
Adverse events resulting in all study drugs discontinued	15 (9)	15 (12)	10 (16)	16 (9)	17 (12)	13 (28)
On-study death	5 (3)	7 (6)	5 (8)	6 (4)	1 (<1)	5 (11)

A similar pattern to the ixazomib arm in the pivotal study was observed in the overall safety analysis population.

Table 57. Summary of Treatment-Emergent Adverse Events by Age: Study C16010 Safety Population

	n (%)							
	Placebo+LenDex N=360				**Ixazomib+LenDex N=360**			
	Age Group in Years				**Age Group in Years**			
MedDRA Terms	**<65**	**65-74**	**75-84**	**≥85**	**<65**	**65-74**	**75-84**	**≥85**
Analysis set: Safety Population	**N=155**	**N=135**	**N=64**	**N=6**	**N=149**	**N=153**	**N=54**	**N=4**
Any AE	153 (99)	133 (99)	63 (98)	6 (100)	141 (95)	152 (99)	54 (100)	4 (100)
Any SAE	59 (38)	63 (47)	38 (59)	3 (50)	55 (37)	68 (44)	23 (43)	1 (25)
Fatal	6 (4)	8 (6)	5 (8)	0	8 (5)	5 (3)	5 (9)	0
Hospitalization/ prolong existing hospitalization[a]	56 (36)	60 (44)	36 (56)	3 (50)	48 (32)	63 (41)	23(43)	1 (25)
Life-threatening	6 (4)	3 (2)	2 (3)	0	1 (<1)	5 (3)	3 (6)	0

	n (%)							
	Placebo+LenDex N=360				Ixazomib+LenDex N=360			
	Age Group in Years				Age Group in Years			
MedDRA Terms	**<65**	**65-74**	**75-84**	**≥85**	**<65**	**65-74**	**75-84**	**≥85**
Analysis set: Safety Population	**N=155**	**N=135**	**N=64**	**N=6**	**N=149**	**N=153**	**N=54**	**N=4**
Disability/incapacity		1 (<1)		0		3 (2)		0
Other (medically significant)	23 (15)	26 (19)	11 (17)	0	22 (15)	25 (16)	11 (20)	0
AE leading to drop out[b]	12 (8)	16 (12)	11 (17)		16 (11)	14 (9)	16 (30)	
Psychiatric disorders	56 (36)	51 (38)	24 (38)	2 (33)	44 (30)	61 (40)	12 (22)	2 (50)
Nervous system disorders	84 (54)	75 (56)	37 (58)	1 (17)	70 (47)	105 (69)	34 (63)	3 (75)
Accidents and injuries	28 (18)	30 (22)	22 (34)		28 (19)	32 (21)	15 (28)	
Cardiac disorders	17 (11)	22 (16)	12 (19)	0	18 (12)	23 (15)	10 (19)	0
Vascular disorders	25 (16)	35 (26)	13 (20)		21 (14)	40 (26)	13 (24)	
Cerebrovascular disorders	0	1 (<1)	3 (5)	0	0	1 (<1)	1 (2)	0
Infections and infestations	106 (68)	100 (74)	40 (63)	3 (50)	96 (64)	124 (81)	36 (67)	3 (75)
Anticholingeric syndrome	0	0	0	0	0	0	0	0
Quality of life:								
Quality of life decreased (TEAE)	0	0	0	0	0	0	0	0
Quality of life decreased[c]	76 (49)	75 (56)	32 (50)	2 (33)	84 (56)	103 (67)	31 (57)	1 (25)
Quality of life improvement (by 5 or more points)	94 (61)	92 (68)	35 (55)	5 (83)	89 (60)	94 (61)	29 (54)	3 (75)
Quality of life improvement (by 10 or more points)	77 (50)	69 (51)	25 (39)		77 (52)	67 (44)	24 (44)	
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[d]	34 (22)	30 (22)	17 (27)		36 (24)	45 (29)	18 (33)	
Other AEs appearing more frequently in older patients								
Rash	38 (25)	27 (20)	8 (13)	2 (33)	47 (32)	52 (34)	23 (43)	3 (75)
Thrombocytopenia	18 (12)	23 (17)	8 (13)	1 (17)	34 (23)	43 (28)	20 (37)	2 (50)

Note: Shaded cells denote data removed to protect the scientific integrity of this ongoing blinded trial.
a. Health utilization measures as reported in C16010 CSR in Module 5, suggest higher emergency room stays, and similar ICU stays, but less hospitalization, acute care stays, outpatient visit, physician/clinic visits in patients treated with the ixazomib regimen as compared to those treated with the placebo regimen.
b. Dropout = AEs leading to discontinuation of the entire study drug regimen.
c. Based on C16010 Phase 3 trial and reported results from questionnaires EORTC QLQ-C30. A patient's quality of life is measured using the EORTC Q30 global score. A decreased quality of life is defined as a negative change from baseline of 10 or more points. An improved quality of life is defined both by a positive change from baseline of 10 or more points and 5 or more points.
d.Totals represent numbers of individual patients with one or more of these TEAEs.

Sex

The safety profile was similar in both genders except that a higher incidence of AE in female patients (vs males) that led to dose reduction (63% vs 44%) or modification (77% vs 66%) was noted in the

ixazomib arm of pivotal study but not in placebo arm. This difference was smaller in the overall safety analysis population.

Race

In the ixazomib regimen in the pivotal study, the frequency of SAEs and AEs leading to discontinuation of the study drug regimen was higher in white patients than Asian, similar to the placebo arm. No other significant differences were noted.

Safety related to drug-drug interactions and other interactions

No data has been submitted.

Discontinuation due to adverse events

Discontinuation of 1 or more of the 3 agents in each regimen or the full study regimen was similar between the two arms in the pivotal study at both cut off data:

	30/10/2014		12/07/2015	
	Placebo+ LenDex N=360	**Ixazomib+ LenDex N=360**	**Placebo+ LenDex N=359**	**Ixazomib+ LenDex N=361**
TEAE resulting in discontinuation of 1 or more of the 3 agents in the study drug regimen	62 (17)	70 (19)	73(20)	91 (25)
TEAE resulting in discontinuation of the full study drug regimen	39 (11)	46 (13)	50 (14)	60 (17)

It should be noted some of these AE were due to disease progression that was captured according to the protocol as TEAE leading to discontinuation.

TEAEs leading to discontinuation of 1 or more agents occurring in ≥1% patients in either arm (but not > 2%) were asthenic conditions, heart failure, peripheral neuropathies, diarrhoea (excluding infective) and sleep disturbances.

The most frequent causes of TEAEs leading to discontinuation of full study regimen were haematological (thrombocytopenia, neutropenia), gastrointestinal (diarrhoea, decreased appetite), general (asthenia, fatigue), neuropathy, and infections.

The timing of study treatment discontinuation in the ixazomib and placebo regimens was comparable, higher in the first 6 cycles and decreased over time.

Post marketing experience

N/A.

2.6.1. Discussion on clinical safety

Ixazomib in combination with lenalidomide and dexamethasone at the proposed dose and schedule has been assessed in 460 MM patients out of whom 360 represent the target population of MM patients who have received at least one prior therapy. Additional data in patients who have received oral ixazomib with different posology, indications or as single agent, contribute to the safety evaluation of ixazomib. Overall, the size of the safety database is considered sufficient to allow adequate assessment of the safety profile.

The safety evaluation is focused primarily on the pivotal study results.

The safety profile of the combination ixazomib + lenalidomide + dexamethasone was overall similar to that seen with lenalidomide +dexamethasone, and patients received a median of 12 cycles of treatment. Most of the AE tend to occur at the beginning of the treatment and declined with continued exposure.

The most frequently reported adverse reactions (≥ 20%) across 360 patients treated each within the ixazomib and placebo regimens in the pivotal clinical trial were diarrhoea (42% vs. 36%), constipation (34% vs. 25%), thrombocytopenia (28% vs. 14%), peripheral neuropathy (28% vs. 21%), nausea (26% vs. 21%), peripheral oedema (25% vs. 18%), vomiting (22% vs. 11%), and back pain (21% vs. 16%).

In the pivotal Phase 3 trial, the following adverse reactions occurred with a similar rate between the NINLARO and placebo regimens: fatigue (28% vs. 26%), neutropenia (30% vs. 27%), decreased appetite (13% vs. 9%), hypotension (5% vs. 4%), heart failure (4% vs. 3%), arrhythmia (13% each), and liver impairment including enzyme changes (6% vs. 5%).

The addition of ixazomib to the backbone standard lendex results in an increase in gastrointestinal AE, peripheral oedema, thrombocytopenia, and maculopapular rash but primarily due to a higher frequency of low grade events except for thrombocytopenia, which had a difference in frequency across all grades. However, potential consequences of thrombocytopaenia like bleeding (18% ixazomib vs 16% placebo for all grades; 2% ixazomib vs <1% placebo for grade 3 or higher), and the need for platelet transfusions (6% ixazomib vs 5% placebo) were similar in both arms. Thrombocytopaenia was a transient, predictable and manageable event.

Only 20% of patients needed at least one dose reduction of ixazomib, and 3% needed the dose reduction twice, and therefore the treatment seems well tolerated.

A trend for grade 3 or 4 AE or AE that resulted in dose modification was noted for older subgroup of patients but probably reflects the effect of age itself and not the addition of ixazomib as it were also seen in the control arm of the pivotal study.

Serious adverse reactions reported in ≥ 2% of patients included thrombocytopenia (2%) and diarrhoea (2%). Overall serious adverse events occurred with similar frequency and type of event across the two arms of the pivotal study and pneumonia was the most frequently reported.

Outside of the Phase 3 study, the following serious adverse reactions were rarely reported: acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumour lysis syndrome and thrombotic thrombocytopenic purpura.

Antiviral prophylaxis should be considered in patients being treated with Ninlaro to decrease the risk of herpes zoster reactivation. Patients included in studies with ninlaro who received antiviral prophylaxis had a lower incidence of herpes zoster infection compared to patients who did not receive prophylaxis.

The potential risk of thromboembolism expected in combination with lenalidomide is not increased, probably because the majority of patients in the pivotal study had received thromboprophylaxis. Thrombocytopenia has been reported with ixazomib with platelet nadirs typically occurring between Days 14-21 of each 28 day cycle and recovery to baseline by the start of the next cycle. Platelet counts should be monitored at least monthly during ixazomib treatment. More frequent monitoring should be considered during the first three cycles as per the lenalidomide SmPC. Thrombocytopenia can be managed with dose modifications and platelet transfusions as per standard medical guidelines.

Diarrhoea, constipation, nausea and vomiting have been reported with ixazomib, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products and supportive care. The dose should be adjusted for severe (Grade 3–4) symptoms.

No safety concern has been identified with regards to new primary malignancies but long term safety data is needed. Appropriate handling of this as proposed in the RMP is considered sufficient.

Fungal and viral pneumonia resulting in fatal outcome were rarely reported in patients given the ixazomib, lenalidomide and dexamethasone combination.

Non clinical data showed a potential for irreversible peripheral nervous system effects. As a proteasome inhibitor ixazomib does not cause concern with regards to neuropathy. Although there was a mild increase in peripheral neuropathy with ixazomib regimen compared to placebo (28% ixazomib vs 21% placebo), it was mainly due to low grade events and led to drug discontinuation in a small number of patients in each arm. However, more mature data is needed to confirm that peripheral neuropathy toxicity is not increased in the long term as patients will be recommended to take the triplet combination until disease progression or unacceptable toxicity.

It appears that gastrointestinal toxicity, peripheral neuropathy and thrombocytopenia seen in the proposed ixazomib combination are of lower frequency than that reported for bortezomib, although there is no available direct comparison between the two proteasome inhibitors. It appears that ixazomib has no worse safety profile than bortezomib.

No other concerns have been raised for adverse events associated with other proteasome inhibitors or lenalidomide.

The discontinuation rate of 1 or more drugs or the full drug combination in the ixazomib regimen is similar to that seen in the placebo control and indicate that adding ixazomib to lenalidomide and dexamethasone does not result in a significant increase in toxicity.

A consistent similar safety profile to the ixazomib regimen in the pivotal study was seen in the overall safety analysis which included patients dosed with oral ixazomib (either as single agent or in combination with other agents) across a range of indications.

There are no data on the effect of ixazomib on the ability to drive or operate machinery. Fatigue and dizziness have been observed in clinical trials. Patients should be advised not to drive or operate machines if they experience any of these symptoms.

There is no known specific antidote for ixazomib overdose. Clinical data is limited but doses up to 12 mg have been reported in the randomized controlled trial. In the event of an overdose, monitor the patient for adverse reactions and provide appropriate supportive care.

No major safety concerns have been identified.

2.6.2. Conclusions on the clinical safety

The safety profile of the proposed treatment regimen with ixazomib as add-on to lenalidomide and dexamethasone is considered acceptable with gastrointestinal (diarrhoea, constipation, nausea, vomiting), haematological (anaemia, neutropenia, thrombocytopenia), fatigue, peripheral oedema, back pain and nasopharyngitis being the most common adverse events.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Thrombocytopenia Severe gastrointestinal events (specifically nausea, vomiting, diarrhoea) Peripheral neuropathy
Important potential risks	Severe dermal events Herpes zoster infections Posterior reversible encephalopathy syndrome
Missing information	Use in pregnancy/ lactation Long-term safety

Pharmacovigilance plan

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
C16010 [Category 3] A Phase 3, Randomized, Double-Blind, Multicenter Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma	The safety objective is to determine the safety of the addition of ixazomib to lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with RRMM.	Long-term safety	Ongoing As of 01 June 2015, 722 patients have been randomized in the study.	CSR for primary endpoint analysis July 2015 CSR addendum (end of study), anticipated December 2019

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
C16019 [Category 3] A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant	The safety objective is to determine the long-term safety and tolerability of ixazomib administration to patients with MM following ASCT.	Long-term safety	Ongoing As of 01 June 2015, 236 patients have been randomized in the study.	CSR for primary endpoint analysis December 2018 CSR addendum (end of study), TBD

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Thrombocytopenia	*SmPC Section 4.2 Posology and method of administration:* Prior to initiating a new cycle of therapy, platelet count should be ≥75,000/mm^3 Specific dose modifications for thrombocytopenia are also discussed. *SmPC Section 4.4 Special warnings and precautions for use:* <u>Thrombocytopenia</u> Thrombocytopenia has been reported with NINLARO (see section 4.8) with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle (see section 4.8). Platelet counts should be monitored at least monthly during NINLARO treatment. More frequent monitoring should be considered during the first three cycles as per the lenalidomide SmPC. Thrombocytopenia can be managed with dose modifications (see section 4.2) and platelet transfusions as per standard medical guidelines. *SmPC Section 4.8 Undesirable effects:* Thrombocytopenia is included as one of the most frequently reported adverse reactions for NINLARO and is listed in the adverse reactions table. <u>Thrombocytopenia</u> Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤10,000/mm^3 during treatment. Less than 1% of patients in both regimens had a platelet count ≤5000/mm^3 during treatment. Thrombocytopenia resulted in discontinuation of one or more of the three drugs in <1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Thrombocytopenia did not result in an increase in hemorrhagic events or platelet transfusions.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Severe gastrointestinal events (specifically nausea, vomiting, diarrhoea)	*Section 4.4 Special warnings and precautions for use:* Gastrointestinal toxicities Diarrhoea, constipation, nausea and vomiting have been reported with NINLARO, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products, and supportive care (see section 4.8). The dose should be adjusted for severe (Grade 3-4) symptoms (see sections 4.2). *SmPC Section 4.8 Undesirable effects:* Nausea, vomiting, and diarrhoea are included among the most frequently reported adverse reactions for NINLARO and are listed in the adverse reactions table. Gastrointestinal Toxicities Diarrhoea resulted in discontinuation of one or more of the three drugs in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen.	None
Peripheral neuropathy	*SmPC Section 4.2 Posology and method of administration:* Specific dose modifications for peripheral neuropathy are discussed. *SmPC Section 4.8 Undesirable effects:* Peripheral neuropathy is included as one of the most frequently reported adverse reactions for NINLARO and is listed in the adverse reactions table. Peripheral neuropathy Peripheral neuropathy occurred in 28% of patients in teh NINLARO regimen compared to 21% of patients in the placebo regimen. Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 1% of patients in both regimens.	None
Severe dermal events	*SmPC Section 4.8 Undesirable effects:* Outside of the Phase 3 study, the following serious adverse reactions were rarely reported: acute febrile neutrophilic dermatosis (Sweet's syndrome) and Stevens-Johnson syndrome.	None
Herpes zoster infections	*SmPC Section 4.2 Posology and method of administration:* Antiviral prophylaxis should be considered in patients being treated with NINLARO to decrease the risk of herpes zoster reactivation. Patients included in studies with NINLARO who received antiviral prophylaxis had a lower incidence of herpes zoster infection compared to patients who did not receive prophylaxis.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	SmPC Section 4.8 Undesirable effects: Herpes zoster is listed in the adverse reactions table.	
Posterior reversible encephalopathy syndrome	*SmPC Section 4.8 Undesirable effects:* Outside of the Phase 3 study, the following serious adverse reactions were rarely reported: posterior reversible encephalopathy syndrome.	None
Use in pregnancy / lactation	*SmPC Section 4.4 Special warnings and precautions for use*: <u>Pregnancy</u> Women should avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential must use highly effective contraception while taking NINLARO and for 90 days after stopping treatment (see section 4.5 and 4.6). Women using hormonal contraceptives should additionally use a barrier method of contraception. *SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction* <u>Oral Contraceptives</u> When ixazomib is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of oral contraceptives needs to be considered. Women using hormonal contraceptives should additionally use a barrier method of contraception. *SmPC Section 4.6 Fertility, pregnancy and lactation:* <u>Pregnancy</u> <u>Women of childbearing potential / Contraception in males and female</u> Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment. When NINLARO is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of oral contraceptives needs to be considered. Women using oral hormonal contraceptives should additionally use a barrier method of contraception. NINLARO can cause foetal harm when administered to a pregnant woman. Women should avoid becoming pregnant while being treated with NINLARO. There are no data for the use of NINLARO in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). NINLARO is not recommended during pregnancy and	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	in women of childbearing potential not using contraception. Breast-feeding It is unknown whether NINLARO/metabolites are excreted in human milk. No animal data are available. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued. Fertility Fertility studies have not been conducted with NINLARO (see section 5.3).	
Long-term safety	None	None

Conclusion

The CHMP and PRAC, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The ixazomib triplet regimen had a 35% improvement in the primary endpoint PFS compared to placebo regimen and reached a statistically significant difference (Median PFS 20.6 months Ixazomib vs 14.7 months placebo; HR=0.742; 95% CI: 0.587, 0.939; p=0.012).

Progression Free Survival analysis in all subgroups populations was in favour of Ixazomib regimen (HR<1), including subgroups with adverse prognostic factors and across all ages, with the exception of patients with baseline creatinine clearance < 60/ml/min (HR 1.032).

Progression Free Survival in the combined high-risk subgroup of patients with del(17), t(4;14), and t(14;16) was in favour of Ixazomib regimen (median PFS 21.4 months in the ixazomib versus 9.7 months in the placebo; HR=0.543; p=0.021).

Progression Free Survival in patients with del (17) who are considered the ultra-high-risk group was in favour of ixazomib regimen (median 21.4 months ixazomib vs 9.7 months placebo; HR=0.596; p=0.162).

Overall Survival favours the ixazomib regimen (median OS not reached in either arm; HR=0.900; 95% CI: 0.615, 1.316).

Overall Survival in patients with deletion chromosome 17 who are considered the ultra-high risk patient population, reported a 49% reduction in risk of death for the ixazomib regimen (HR 0.506) and an 18 month survival rate of 86% for ixazomib regimen vs 67% with placebo.

The ixazomib regimen delayed the time to disease progression by approximately 6 months (median TTP 21.4 months in the ixazomib arm vs 15.7 months in the placebo arm; HR=0.712; CI 0.556, 0.912; p=0.007).

Response to treatment was reported with statistically significant difference in favour of ixazomib regimen, including overall response rate CR+PR (OR= 1.44 (1.03, 2.03), p=0.035), CR+VGPR (OR= 1.45 (1.08, 1.95), p=0.014) and CR (OR= 1.87 (1.10, 3.16), p=0.019).

Duration of response to treatment is longer with ixazomib regimen with median DOR 20.5 months ixazomib (16.62, NE) vs 15.0 m placebo (11.99, NE).

The subgroup of patients who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+]; or experienced at least 2 relapses) reported a median PFS benefit of 6.2 months: 18.4 months in the ixazomib regimen versus 12.2 months in the placebo regimen at the primary analysis (HR= 0.700 [p=0.009]), and at the updated analysis a median PFS benefit of 6 months (18.9 months vs 12.9 months; HR=0.745 [p=0.015]).

Uncertainty in the knowledge about the beneficial effects

Efficacy data is based on a planned interim analysis (data cut-off October 2014) where the statistical evidence for the primary endpoint (p=0.012) achieved the pre-specified threshold for claiming benefit at the interim (p<0.0163). The result is not considered compelling for a single pivotal study (replicating the evidence from two trials positive at p<0.05 a P<0.00125 would be required).

Updated efficacy data from a second interim analysis representing the most up-to date data, showed a reduced difference in effect between arms in the overall ITT population for PFS, response rates and time to progression compared to previous analysis. The hazard ratio (95% CI) for the updated PFS analysis was 0.818 (0.67, 1.0) compared to 0.742 (0.587, 0.939) as seen previously.

It is not possible to identify a higher-risk subgroup that could benefit from treatment with ixazomib, especially based on post-hoc analysis and in view of non-compelling overall results. In addition, the results for the primary analysis and for sub-groups worsen from the first interim analysis to the second interim analysis and where the better results seen in high-risk patients appeared to be driven by patients with del(17) in the first interim analysis, but seemed driven by those with t(4;14) in the second interim analysis.

Some regional differences were noted, and in Japan, a better PFS outcome was reported in the placebo arm compared with the ixazomib arm (HR 1.327) which may be due to baseline disease differences compared to the global ITT population.

Median OS is not evaluable yet and the data is considered immature. Further analysis on longer follow up is needed to exclude a detrimental impact on OS with Ixazomib regimen.

In adult patients with multiple myeloma who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+]; or experienced at least 2 relapses) there is a lack of clinical rationale for post hoc arguments that efficacy is greater in this population. There is substantial uncertainty associated with the interpretation of post hoc subgroup analyses, including a number of inconsistencies in the data regarding risk factors for early progression. Analyses in this subgroup were not statistically compelling and differences from the overall ITT population are considered likely to be chance findings.

Risks

Unfavourable effects

The most frequently reported adverse reactions (≥ 20%) across 360 patients treated each within the ixazomib and placebo regimens in the pivotal clinical trial were diarrhoea (45% vs. 39%), constipation (35% vs. 26%), thrombocytopenia (24% vs. 11%), peripheral neuropathy (28% vs. 21%), nausea (29% vs. 22%), peripheral oedema (28% vs. 20%), vomiting (23% vs. 12%), and back pain (24% vs. 17%).

Thrombocytopaenia is reported in 20% of patients receiving the Ixazomib regimen (vs 10% placebo) with the difference between the two regimens across all grades, including Grade 3/4 (17% ixazomib and 8% placebo). All grades of bleeding [18% ixazomib and 16% placebo], Grade 3 or higher bleeding [2% ixazomib and <1% placebo], and need for platelet transfusions [6% ixazomib and 5% placebo] were reported. Thrombocytopaenia with ixazomib regimen has a nadir at day 14-21 of the treatment cycle, is predictable, reversible and manageable with supportive care and platelet transfusion.

There is an increase in gastrointestinal toxicity with ixazomib regimen compared to placebo regimen (74% vs 68%), specifically for diarrhoea (45% vs 39%), nausea (29% vs 22%) and vomiting (24% vs 11%). The majority of events were of low grade and diarrhoea was the only AE that occurred as a grade 3 in at least 5% of patients with Ixazomib (6% ixazomib vs 3% placebo). No grade 4 events were reported. Nausea or vomiting did not result in drug discontinuation while diarrhoea led to treatment discontinuation (1 or more agents in combination) in 5 patients in ixazomib regimen (vs 3 patients in placebo). The gastrointestinal toxicity is managed and some events may be prevented with supportive care (e. g. antiemetics).

The incidence of peripheral neuropathy was 28% in the ixazomib regimen and 21% in the placebo mostly of Grade 1 or 2. The most commonly peripheral neuropathy reported was sensory. Both regimens had a 2% incidence of Grade 3 peripheral neuropathy events and no grade 4 events were reported. Discontinuations of ≥1 of the agents in the study drug regimen were infrequent (1% in each regimen).

Uncertainty in the knowledge about the unfavourable effects

There are no important uncertainties in the knowledge of unfavourable effects.

Effects table

Table 58. Effects Table for Ninlaro (ixazomib) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy (data cut-off:30 October 2014 (1st IA) and 12 July 2015 (2nd IA)

Effect [1]	Short Description	Unit	Treatment	Control	Uncertainties/ Strength evidence	References
Favourable Effects						
PFS 1st IA	Median 95% CI	months	20.6 (17.02, NE)	14.7 (12.91, 17.58)	Strength of evidence not sufficiently high for a single pivotal trial	Discussion on clinical efficacy (CHMP AR)
		HR 0.742 (0.587, 0.939) p=0.012				
PFS 2nd IA	Median 95% CI	months	20.0 (17.97, 23.43)	15.9 (13.21, 18.83)	Reduced efficacy difference between arms from previous analysis. Statistical evidence not compelling for single pivotal trial application Some regional differences (Japan region ixazomib regimen shorter PFS versus placebo)	
		HR 0.818 (0.67, 1.0) p=0.054				
OS 2nd IA	Median		NE	NE	Immature data.	
		HR 0.868 (0.642, 1.175) p=0.359				
PFS high risk patients 2nd IA	Median	months	18.7	9.3	Results in favour for ixazomib are not significantly changed between 1st and 2nd IA Uncertainty for high risk patients benefit as 1st IA positive results driven mainly by results in del 17 patients whilst in 2nd IA they are driven by the patients with t(4:14).	
		HR 0.625 (p=0.037)				
PFS patients with del 17 2nd IA	Median	months	15.7	9.7		
		HR 0.82 (p=0.055)				
ORR 2nd IA	% P= 0.089		78.6	73.2	No statistical significant difference in ORR at 2nd IA that was previously seen in 1st IA	
DOR	Median	months	26	21.7		
TTP	Median	months	22.4	17.6		
PFS Subgroup of 1 prior therapy and adverse risk characterisics, or after 2 prior therapies 1st IA	Median	months	18.4 HR 0.700 (p 0.009) 18.9 HR 0.745	12.2 12.9	Terminolgy "adverse risk" is too broad No benefit seen in other poor risk subgroups (e.gf > 75 years, ECOG 2)	

Effect [1]	Short Description	Unit	Treatment	Control	Uncertainties/ Strength evidence	References
2nd IA			(p 0.015)			
Unfavourable Effects						
Thrombocytopaenia	Incidence	%	24	11	No uncertainties	Discussion on clinical safety (CHMP AR)
Nausea	Incidence	%	29	22		
Vomiting	Incidence	%	23	12		
Diarrhoea	Incidence	%	45	39		
Constipation	Incidence	%	35	26		

Abbreviations: AE: adverse event, AR: Assessment Report, CI: confidence interval, CR: complete response, DOR: duration of response, HR: Hazard Ratio, IA: interim Analysis, KM: Kaplan Meier, NE: Not estimated, ORR: overall response rate, OS: overall survival, PFS: progression free survival, TTP: time to progression.

Benefit-risk balance

Importance of favourable and unfavourable effects

At the first interim analysis of the pivotal study, a 6 months improvement in PFS was reported when ixazomib was added to the standard Lendex regimen. This PFS improvement was considered clinically meaningful and significant, especially as it showed a consistent benefit in patients with high risk cytogenetic abnormalities, across subgroups, and other endpoints. However the statistical approach was not as rigorous as expected in an application with a single pivotal study. The second interim analysis including more mature data has shown a reduced difference in effect between arms in the overall ITT population for PFS, response rates and time to progression compared to previous analysis. This is of major concern, especially in an application based on a single pivotal study.

The Applicant has tried to identify a subpopulation of patients with poor prognosis in whom the efficacy of ixazomib can be demonstrated and proposed the indication for the treatment in patients with one prior therapy and adverse risk characteristics, or for patients after two prior therapies. The terminology of adverse risk characteristics is considered too broad. Data in some subgroups with adverse risk characteristics did not show add on benefit of ixazomib and restriction by line of therapy may not be appropriate due to the high heterogeneity in terms of prior treatments. The results from the ITT population are not impressive and there is substantial uncertainty associated with the interpretation of post hoc subgroup analyses. In addition the results worsen from the first to the second interim analysis for these subgroups and for the overall ITT population.

More mature data is needed to exclude any detrimental effect on survival.

Benefit-risk balance

The benefit-risk balance for ixazomib for the treatment of adult patients with multiple myeloma who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+]; or experienced at least 2 relapses is considered negative.

Discussion on the benefit-risk balance

Efficacy data remains insufficient for approval in the proposed subgroup of patients. It is unknown what drives the benefits in some particular subgroups and there is no clinical rationale. Efficacy data in the overall ITT population does not provide the level of evidence expected on an application based on a single pivotal trial and there is still large uncertainty associated with the interpretation of subgroup analysis.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ninlaro is not similar to Thalidomide Celgene, Revlimid, Imnovid, Farydak, Kyprolis and Daratumumab within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy for NINLARO in the treatment of adult patients with multiple myeloma who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+]; or experienced at least 2 relapses the CHMP considers by consensus that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

The evidence of efficacy in the proposed indicated patient populations (adult patients with multiple myeloma who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+]; or experienced at least 2 relapses) is considered insufficient. The data are currently immature, especially for overall survival which is not yet evaluable. Efficacy data in the overall ITT population from the first and second interim analyses do not provide the statistically compelling evidence expected for an application based on a single pivotal trial. Point estimates for efficacy measures are not sufficiently outstanding in the context of other available treatment options. There is a lack of clinical rationale for post hoc arguments that efficacy is greater in the higher risk subgroups proposed for the revised indications. There is substantial uncertainty associated with the interpretation of post hoc subgroup analyses, including a number of inconsistencies in the data regarding risk factors for early progression. Analyses in these subgroups were not statistically compelling and differences from the overall ITT population are considered likely to be chance findings.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and post-authorisation measures cannot be agreed at this stage.

New Active Substance Status

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

5. Re-examination of the CHMP opinion of 26 May 2016

Following the CHMP conclusion that Ninlaro was not approvable based on the efficacy grounds outlined

above, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented detailed grounds for re-examination in writing and at an oral explanation.

A summary of the applicant's grounds for re-examination is presented below.

Clinical Ground No. 1 (Efficacy data in the overall ITT population from the first and second interim analyses do not provide the statistically compelling evidence expected for an application based on a single pivotal trial).

The applicant argued that the efficacy data in Study C16010—from both interim analyses (IAs)—do provide statistically compelling evidence, with confirmation in a second study, the China Continuation study. In Study C16010, the pre-specified boundary was crossed at the planned first PFS analysis, thus making the first IA the final analysis for PFS for statistical testing purposes. However, the study was not stopped after the first IA because the long-term endpoint of OS, an important secondary endpoint, was continuing to be followed. Because the study was to continue in a blind fashion, the FDA requested that the applicant take the opportunity to conduct a non-inferential sensitivity analysis for PFS at the planned second IA, which was supposed to focus on OS. In a normal group sequential design setting, the applicant would not have performed another analysis for PFS, and there would be no second IA data for PFS for Study C16010 had it not had continued the study for the key secondary endpoint (OS). According to the applicant the basis of Study C16010 design, the first IA (date cut-off date, October 2014, median follow-up of 15 months) is the primary analysis for PFS, as pre-specified more stringent criteria has been met; the second IA (data cut-off date, July 2015, median follow up of 23 months) is only a sensitivity analysis for PFS and should be interpreted as such.

Clinical Ground No. 2 (There is substantial uncertainty associated with the interpretation of post-hoc subgroup analyses, including a number of inconsistencies in the data regarding risk factors for early progression; analyses in these subgroups were not statistically compelling and differences from the overall ITT population are considered likely to be chance findings).

The applicant modified the applied indication: ''Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with MM who have received at least 2 prior therapies and are not refractory to lenalidomide or proteasome inhibitors''. The applicant considered the proposed subgroup with at least 2 prior therapies, as ascertained as a stratification factor, to be an appropriate, robust subgroup to propose as the indication population. According to the applicant, the subgroup is pre-specified with its analyses conducted on the basis of the ITT principle, the patient and disease characteristics are well balanced between the treatment regimens, and the findings for the subgroup are robust against being due to chance. The applicant argued that this subgroup is relatively large (41% of the ITT population), has a highly significant effect size, meets the definition of a credible subgroup and shows a PFS benefit (HR 0.580, p=0.003, at the primary analysis, and HR=0.617, p=0.003, at the non-inferential analysis (July 2015) with a median of 9 months) with the ixazomib+LenDex that is mature, consistent between the 2 analyses, indicates a positive risk-benefit profile, supported by investigator-determined data and secondary efficacy endpoints, and confirmed in the China Continuation study.

Clinical Ground No. 3 (The evidence of efficacy in the proposed indicated patient populations (adult patients with multiple myeloma who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+], or experienced at least 2 relapses) is considered insufficient; the data are currently immature, especially for overall survival which is not yet evaluable).

As mentioned above (clinical ground No. 2) the applicant modified the applied indication and considered that in the subgroup of patients who have been previously treated with at least 2 prior therapies, the PFS benefit with the ixazomib regimen is consistent across the follow up periods and is mature. Further, the PFS benefit is accompanied by high response rates and a trend toward an OS advantage. This efficacy benefit was not accompanied by substantial additional toxicity, which allows for long-term treatment and disease control. Additionally patient reported QOL (per EORTC QLQ-C30 or EQ-5D scores) was maintained. These data are notable given the context of a double-blind, placebo-controlled study. The efficacy benefit with the better safety profile of the ixazomib regimen combined with the benefit of an all oral dosing regimen offers patients the opportunity to work and live, almost normally, while effectively controlling their disease. This provides an important contribution to the care of patients with MM.

Clinical Ground No. 4 (There is a lack of clinical rationale for post-hoc arguments that efficacy is greater in the higher-risk subgroups proposed for the revised indication).

On the basis of preliminary analyses and a review of the literature, the applicant posited the hypothesis that the subgroup of patients with at least 2 prior therapies has increased sensitivity to ixazomib because of a number of factors, including the clinical features of these patients and the evolution of MM clones that are more sensitive to proteasome inhibitors. One important mechanism by which ixazomib+LenDex appears to overcome the negative prognosis associated with 2 or more prior therapies may rest in the ability to target MM clones with increased genome instability and aggressiveness, such as overexpression of the gene MYC (Deshaies RJ. , 2014). The fact that IMiDs work better when used earlier in the course of disease, (Stadtmauer EA, et al. 2009) where a more limited repertoire of abnormalities are present, supports the hypothesis of clonal evolution. Previous exposure to IMiDs is very common among the subgroup with at least 2 prior therapies in Study C16010, suggesting placebo+LenDex would have less benefit than ixazomib+LenDex. High MYC expression frequently predicts for aggressive biological behaviour, advanced stage of disease, increased likelihood of relapse, and poor clinical outcome in MM. In Study C16010, MYC expression is higher in the subgroup with at least 2 prior therapies than in the subgroup with 1 prior therapy ($p=0.0164$), and the PFS benefit for the ixazomib regimen versus the placebo regimen is significantly higher among patients whose tumours express c-MYC levels above the median. In tumours with already high MYC expression, proteasome inhibition may further increase MYC expression, leading to induction of cell death.

Clinical Ground No. 5 (Positive benefit-risk profile of the ixazomib regimen for the subgroup with at least 2 prior therapies in the context of other available therapies).

The applicant has performed an historical comparison of the ixazomib regimen with other available therapies. In the proposed indication of patients who received at least 2 prior therapies, the clinical benefit of ixazomib (PFS HR=0.58) compares favourably to other approved combinations: panobinostat HR=0.64, carfilzomib HR=0.69, and elotuzumab HR=0.65. The applicant argued that the safety profile of ixazomib has already been accepted by CHMP and provides needed options, especially for the heterogeneous and comorbid proposed subgroup of patients with at least 2 prior therapies. Further, QOL was maintained in the ixazomib regimen as compared with the placebo regimen, whereas, by contrast, in the PANORAMA-1 study, the panobinostat regimen was associated with significant worsening of QOL. With the caveat of open-label trials that may favour the interventional arm, ELOQUENT-2 reported QOL that was maintained in the elotuzumab regimen and in the ASPIRE study; QOL was higher in the carfilzomib regimen for a few domains.

The applicant concluded that, point estimates associated with ixazomib+LenDex for efficacy measures for the subgroup with at least 2 prior therapies are sufficiently outstanding in the context of other

available treatment options. When safety, tolerability, QOL, and impact on health care utilization are considered along with efficacy, the benefit-risk profile of ixazomib+LenDex compares favourably with those of other available therapies for RRMM.

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

Report from the SAG

As a general comment, the SAG considered unanimously that the data submitted on the basis of the primary ITT analysis of PFS of the pivotal trial C16010 (HR=0.742; *P*=0.012), and, importantly, the favourable toxicity profile, establish a clearly positive benefit-risk balance in the broad indication consistent with the studies' main entry criteria (patients with multiple myeloma who have received at least one prior therapy, see patient characteristics of trial C16010).

The SAG discussed the concerns that have been raised about efficacy, due to the results of a subsequent analysis of PFS showing a reduced statistical significance. However, the SAG considered that on the basis of the primary PFS analysis, which was conducted according to the pre-specified statistical considerations, the trial met its objective of showing a statistically and clinically significant improvement in PFS. In terms of primary statistical procedure, the planned final test (2014) at 286 IRC PFS events (i.e., 40% of patients progressed) was significant at the designated point.

The maturity of the dataset was considered adequate and consistent with other pivotal trials in this setting. Additionally, the supportive data from the China Continuation Study provided corroborative findings in terms of a statistical and clinically significant effect in terms of PFS (HR=0.598; *P*=0.035). The robustness of this conclusion is also supported by internal consistency, namely, the favourable trends in terms of OS in the pivotal and supportive studies (HR=0.868, *P*=0.36, and HR=0.323, *P*=0.013, respectively), as well as the biological rationale for proteasome inhibitor therapy in multiple myeloma.

The fact that a subsequent exploratory analysis showed some uncertainty about the level of statistical significance is not enough to change the conclusions about a clear beneficial effect in terms of PFS on the basis of the pre-planned analysis. However, it is acknowledged that the size of the effect observed in the primary analysis might be an over-estimation. This uncertainty about the size of the effect has to be weighed into the benefit-risk assessment.

Concerning the benefit-risk assessment and managing uncertainty about magnitude of the effect, it is important to note that ixazomib was associated with a favourable toxicity profile. The incidence of grade 3 or higher adverse events was similar across treatment groups (76% v. 77% for placebo and ixazomib, respectively); the incidence of drug-related serious adverse events was similar across treatment groups (29% v. 28% for placebo and ixazomib, respectively); and there was no detriment in health-related quality of life based on EORTC-QLQ-C30.

Concerning the benefit-risk balance, given the favourable toxicity profile, even in the case of an over-estimation, the SAG was confident that a positive benefit-risk balance has been established. Concerning the possible uncertainty about the magnitude of the effect, this uncertainty seems acceptable given the favourable toxicity profile, and considering that ixazomib is the first agent to allow oral triple combination therapy, which represents a therapeutic innovation in terms of convenience for patients.

These considerations apply to all questions which explore the effect of ixazomib in the subgroups of patients with one or more prior therapies. Although it is acknowledged that in exploratory analyses a

more pronounced effect was observed in patients at higher risk or having 2 or more, or perhaps 3 previous therapies, these findings are based on exploratory subgroup analyses without robust multiplicity adjustment. Thus, there is insufficient evidence to exclude that there is a clinically relevant effect also in patients at lower risk of progression or that had only 1 prior line of therapy.

1. **Are the concerns on the data maturity (PFS and confirmation by OS) still valid?**

The number of events is considered in line with what is generally expected in the field for trials of this size in this population. Hence the ITT analysis is therefore considered mature and the observed effect (about 6 month difference in median PFS) as clinically relevant. Although subsequent analyses showed slightly less statistical significance, this slight fluctuation is not considered to invalidate the conclusions of the primary analysis, based on the totality of the data.

The OS analysis is not considered sufficiently mature and it is also possible that in view of new agents with impact on OS a clear difference in terms of OS might be difficult to observe in the long term. In multiple myeloma in this treatment setting, however, PFS is considered a clinically relevant endpoint and the magnitude of the effect quite significant. In addition, the favourable trend in OS in the ITT populations is promising and one can rule out a detrimental effect on OS with reasonable certainty.

2. **Please discuss in the context of one single pivotal study supported only by the Chinese trial, whether the proposal for a restricted indication based on the choice for the subgroup ≥ 2 prior lines of therapy is acceptable? This also taking into account the arguments of the Applicant and the concept that type of prior treatment may also be relevant for the response to next line treatment.**

The SAG did not agree about drawing firm conclusions based on the post-hoc analyses presented. Although it was acknowledged that these analyses are based on pre-specified stratification factors in the context of an overall positive ITT analysis, and on external validation from another study, it is difficult to assess the significance of these findings without proper multiplicity adjustment. More importantly, although there are a number of plausible hypotheses that could explain this finding, a robust biological rationale has not been identified.

The primary ITT analysis is considered still the most relevant and is statistically and clinically convincing.

The fact that the results are based on a single pivotal trial is not considered an issue in view of the convincing results, the supportive evidence from the China Continuation Study and the entirety of the evidence. Taken together with the limited toxicity and possibility of oral dosing, the uncertainty related to the effect size is not considered enough to outweigh the benefits.

3. **Please discuss in light of other available lenalidomide-based triplet regimens, whether the improvement in median PFS of approximately 9 months in the pre-specified subgroup (≥ 2 prior lines of therapy) indicate clinical benefit in this clinical setting, despite the lack of mature OS data.**

Recently approved drugs for the treatment of multiple myeloma have shown improvements in median in PFS in the range of 4 to 6 months. The 6-months improvement observed in the ITT population clearly and convincingly indicates clinical benefit for this first orally available triple-drug regimen.

4. **Results in the heavily pre-treated population (new claimed indication) contrast with what is observed in patients treated with one previous line only. Is there any rationale to explain this contrast and to exclude that is was produced at least in part by chance?**

This finding is somewhat in contrast with what is observed with other drugs and tumour types where the effect is generally opposite. Thus, the finding from exploratory analyses should be looked at carefully. There are a number of hypotheses possible, including the burden of disease and clonal

developments, the emergence of particular mutations, immunological mechanisms, etc. However, it is difficult to conclude with certainty about any of these hypotheses on the basis of these exploratory analyses.

The level to which the subgroup analysis stands out is a common situation in clinical trial analysis. Any correction for this level of subgroup multiplicity, in absence of a strong a priori rationale for the direction of this finding, would not be statistically significant. For example, one possible correction factor would be 18.

If any opportunistic subgroup would need to be selected on the basis of available data, it would possibly be for 3 prior treatments which is the subgroup that stands out most in the Forest plot, while 2 prior lines is not very different to 1 prior line.

In conclusion, there does not seem to be a strong rationale or statistical evidence to exclude a significant effect also in patients with 1 prior line of treatment. Translational research is ongoing to identify subjects more likely to respond on the basis of mutational and expression analyses (e.g., the oncogene c-myc expression). These data should be thoroughly evaluated when available to inform selection strategies to identify subjects more likely to benefit from ixazomib.

5. Please discuss the potential added value of an all oral treatment regimen like the currently proposed regimen with ixazomib + LenDex in this clinical setting, and please also discuss if this compensates for the observed uncertainties?

Oral dosing is undoubtedly a major added value as ixazomib is the first agent to allow effective oral triple-combination therapy. This should have a major impact in terms of the subjects' convenience, particularly when compared to intravenous treatments requiring frequent visits to the clinic. Any uncertainties about the effect size in terms of OS or PFS are considered acceptable in view of the low toxicity and the additional benefits.

6. Should a potential indication refer to the type of prior treatments (SCT yes or no) in view of the results of the exploratory analyses on the subgroups with prior SCT?

At present, it is difficult to conclude on the basis of exploratory analyses presented. However, the effect did not seem to be dramatically different in these subgroups. Thus, referring to prior treatments (SCT yes of no) does not seem necessary.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group.

Concerning Clinical Ground No. 1, the CHMP considered that the primary endpoint, PFS was met and the result was robust in the first planned interim analysis (IA), 20.6 months in the ixazomib+LenDex regimen versus 14.7 months in the placebo+LenDex regimen (p=0.012 and HR 0.742). However, updated efficacy data from a second interim analysis representing the most up-to date data, showed a reduced difference in effect between arms in the overall ITT population for PFS, response rates and time to progression compared to previous analysis. The hazard ratio (95% CI) for the updated PFS analysis was 0.818 (0.67, 1.0) compared to 0.742 (0.587, 0.939) as seen previously.

The CHMP acknowledged the applicant's argumentations that the second IA is only a sensitivity analysis, and should be interpreted as such and concluded that it is difficult not to acknowledge the positive result of a large clinical trial (n=722) in this clinical setting.

The CHMP, however, noted, that the total avaialable evidence on efficacy is not as comprehensive as normally would be required.

Concerning Clinical Ground No. 2 the CHMP did not agree that there would be sufficient grounds to define the target population in the indication as patients who have received at least 2 prior therapies, as proposed by the applicant since the results are based on post-hoc analyses. The CHMP acknowldged that the number of prior therapies was a pre-specified stratification factor (1 vs. 2-3 therapies) in the SAP. Furthermore the size of this subgroup was considerable (a total of 297 of the 722 patients) and there were no substantial differences between baseline characteristics in the different treatment arms. However, it is not possible to correctly assess the significance of these findings without proper multiplicity adjustment.

In addition, the results in the heavily pre-treated population (new proposed indication) contrast with what is observed in patients treated with one previous line only and there does not seem to be a biological rationale or statistical evidence to exclude a significant effect also in patients with 1 prior line of treatment.

The CHMP therefore considered that the efficacy evidence is equally relevant for the entire population included in the pivotal study, i.e. multiple myeloma patients who have received at least one prior therapy.

Concerning Clinical Ground No. 3 the CHMP opinion remained negative regarding the previous proposed indication. The evidence of efficacy in the proposed patient populations (adult patients with multiple myeloma who have experienced at least one relapse with ISS stage III disease or elevated-risk cytogenetics [del(17), t(4;14), t(14;16), or 1q21+], or experienced at least 2 relapses) is considered insufficient.

Concerning Clinical Ground No. 4 the CHMP acknowledged the several mechanisms that could explain the increased sensitivity to ixazomib in the subgroup of patients with at least two prior therapies, compared to one prior therapy however it is not possible confirm them by obervations in clinical practice.

Therefore the CHMP concluded that there is a lack of clinical rationale to explain the supposed greater efficacy in the higher-risk subgroups, proposed as basis for the revised indication.

Concerning Clinical Ground No. 5 the CHMP concluded that recently approved drugs for the treatment of multiple myeloma have shown improvements in median in PFS in the range of 4 to 6 months; therefore the 5.9 months improvement observed in the ITT population is considered clinically relevant.

5.1. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Thrombocytopenia Severe gastrointestinal events (specifically nausea, vomiting, diarrhoea) Peripheral neuropathy

Important potential risks	Severe dermal events Herpes zoster infections Posterior reversible encephalopathy syndrome
Missing information	Use in pregnancy/ lactation Long-term safety

Pharmacovigilance plan

Study/Activity Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
C16010 [Category 1] A Phase 3, Randomized, Double-Blind Study C16010 in Adult Patients With Relapsed and/or Refractory Multiple Myeloma	The safety objective is to determine the safety of the addition of ixazomib to lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with RRMM.	Long-term safety	Ongoing As of 01 June 2015, 722 patients have been randomized in the study.	December 2019
C16019 [Category 2] A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of ixazomib in Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant	The safety objective is to determine the long-term safety and tolerability of ixazomib administration to patients with MM following ASCT.	Long-term safety	Ongoing As of 01 June 2015, 236 patients have been randomized in the study.	December 2018

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)
**C16010 is listed as a Category 1 study in Part III (PhV Plan) as it is also a Post-authorisation efficacy study (PAES) listed in Part IV (Efficacy development plan) with Imposed obligation.
*** C16019 is listed as a Category 2 study in Part III (PhV Plan) as it is also a Post-authorisation efficacy study (PAES) listed in Part IV (Efficacy development plan) with Specific obligations.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Thrombocytopenia	*SmPC Section 4.2 Posology and method of administration:* Prior to initiating a new cycle of therapy, platelet count should be ≥75,000/mm^3 Specific dose modifications for thrombocytopenia are also discussed. *SmPC Section 4.4 Special warnings and precautions for use:* <u>Thrombocytopenia</u> Thrombocytopenia has been reported with NINLARO (see section 4.8) with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle (see section 4.8). Platelet counts should be monitored at least monthly during NINLARO treatment. More frequent monitoring should be considered during the first three cycles as per the lenalidomide SmPC. Thrombocytopenia can be managed with dose modifications (see section 4.2) and platelet transfusions as per standard medical guidelines. *SmPC Section 4.8 Undesirable effects:* Thrombocytopenia is included as one of the most frequently reported adverse reactions for NINLARO and is listed in the adverse reactions table. <u>Thrombocytopenia</u> Three percent of patients in the NINLARO regimen and 1% of patients in the placebo regimen had a platelet count ≤10,000/mm^3 during treatment. Less than 1% of patients in both regimens had a platelet count ≤5,000/mm^3 during treatment. Thrombocytopenia resulted in discontinuation of one or more of the three medicinal products in <1% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Thrombocytopenia did not result in an increase in haemorrhagic events or platelet transfusions.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Severe gastrointestinal events (specifically nausea, vomiting, diarrhoea)	*SmPC section 4.4 Special warnings and precautions for use:* Gastrointestinal toxicities Diarrhoea, constipation, nausea and vomiting have been reported with NINLARO, occasionally requiring use of antiemetic and antidiarrhoeal medicinal products, and supportive care (see section 4.8). The dose should be adjusted for severe (Grade 3-4) symptoms (see sections 4.2). In case of severe gastrointestinal events, monitoring of serum potassium level is recommended. *SmPC Section 4.8 Undesirable effects:* Nausea, vomiting, and diarrhoea are included among the most frequently reported adverse reactions for NINLARO and are listed in the adverse reactions table. Gastrointestinal Toxicities Diarrhoea resulted in discontinuation of one or more of the three medicinal products in 1% of patients in the NINLARO regimen and < 1% of patients in the placebo regimen.	None
Peripheral neuropathy	*SmPC Section 4.2 Posology and method of administration:* Specific dose modifications for peripheral neuropathy are discussed. *SmPC Section 4.4 Special warnings and precautions for use:* Peripheral neuropathy Peripheral neuropathy has been reported with NINLARO (see section 4.8). The patient should be monitored for symptoms of peripheral neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification (see section 4.2). *SmPC Section 4.8 Undesirable effects:* Peripheral neuropathy is included as one of the most frequently reported adverse reactions for NINLARO and is listed in the adverse reactions table. Peripheral neuropathy Peripheral neuropathy occurred in 28% of patients in	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	teh NINLARO regimen compared to 21% of patients in the placebo regimen. Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens. The most commonly reported reaction was peripheral sensory neuropathy (19% and 14% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three medicinal products in 1% of patients in both regimens.	
Severe dermal events	*SmPC Section 4.4 Special warnings and precautions for use:* Cutaneous reactions Rash has been reported with NINLARO (see section 4.8). Rash should be managed with supportive care or with dose modification if Grade 2 or higher (see section 4.2). *SmPC Section 4.8 Undesirable effects:* Outside of the Phase 3 study, the following serious adverse reactions were rarely reported: acute febrile neutrophilic dermatosis (Sweet's syndrome) and Stevens-Johnson syndrome.	None
Herpes zoster infections	*SmPC Section 4.2 Posology and method of administration:* Antiviral prophylaxis should be considered in patients being treated with NINLARO to decrease the risk of herpes zoster reactivation. Patients included in studies with NINLARO who received antiviral prophylaxis had a lower incidence of herpes zoster infection compared to patients who did not receive prophylaxis. *SmPC Section 4.8 Undesirable effects:* Herpes zoster is listed in the adverse reactions table.	None
Posterior reversible encephalopathy syndrome	*SmPC Section 4.4 Special warnings and precautions for use:* Posterior reversible encephalopathy syndrome Posterior reversible encephalopathy syndrome (PRES) has occurred in patients receiving NINLARO. PRES is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, altered consciousness, and visual disturbances. Brain imaging,	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	preferably Magnetic Resonance Imaging, is used to confirm the diagnosis. In patients developing PRES, discontinue NINLARO. *SmPC Section 4.8 Undesirable effects:* Outside of the Phase 3 study, the following serious adverse reactions were rarely reported: posterior reversible encephalopathy syndrome.	
Use in pregnancy / lactation	*SmPC Section 4.4 Special warnings and precautions for use*: <u>Pregnancy</u> Women should avoid becoming pregnant while being treated with NINLARO. If NINLARO is used during pregnancy or if the patient becomes pregnant while taking NINLARO, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential must use highly effective contraception while taking NINLARO and for 90 days after stopping treatment (see sections 4.5 and 4.6). Women using hormonal contraceptives should additionally use a barrier method of contraception. *SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction* <u>Oral Contraceptives</u> When NINLARO is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of oral contraceptives needs to be considered. Women using oral hormonal contraceptives should additionally use a barrier method of contraception. *SmPC Section 4.6 Fertility, pregnancy and lactation:* As NINLARO is administered in combination with lenalidomide and dexamethasone, refer to the SmPC for these medicinal products for additional information on fertility, pregnancy and lactation. <u>Women of childbearing potential /Contraception in males and females</u> Male and female patients who are able to have children	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	must use effective contraceptive measures during and for 90 days following treatment. NINLARO is not recommended in women of childbearing potential not using contraception. When NINLARO is administered together with dexamethasone, which is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters, the risk for reduced efficacy of oral contraceptives needs to be considered. Therefore,women using oral hormonal contraceptives should additionally use a barrier method of contraception. <u>Pregnancy</u> NINLARO is not recommended during pregnancy as it can cause foetal harm when administered to a pregnant woman. Therefore, women should avoid becoming pregnant while being treated with NINLARO. There are no data for the use of NINLARO in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). NINLARO is given in combination with lenalidomide, Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect in humans is expected. The conditions of the Pregnancy Prevention Programme for lenalidomide must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential. Please refer to the current lenalidomide SmPC. <u>Breast-feeding</u> It is unknown whether NINLARO/or its metabolites are excreted in human milk. No animal data are available. A risk to newborns/infants cannot be excluded and therefore breast-feeding should be discontinued. NINLARO will be given in combination with lenalidomide and breast-feeding should be stopped because of the use of lenalidomide.	

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Fertility Fertility studies have not been conducted with NINLARO (see section 5.3).	
Long-term safety	None	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

5.2. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

5.3. Product information

5.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

5.3.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ninlaro (ixazomib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU, and is to be approved under conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6. Benefit-risk balance

Benefits

Beneficial effects

In pivotal trial, the ixazomib triplet regimen had a 35% improvement in the primary endpoint PFS compared to placebo regimen and reached a statistically significant difference (Median PFS 20.6 months Ixazomib vs 14.7 months placebo; HR=0.742; 95% CI: 0.587, 0.939; p=0.012).

Progression Free Survival analysis in all subgroups populations was in favour of Ixazomib regimen (HR<1), including subgroups with adverse prognostic factors and across all ages, with the exception of patients with baseline creatinine clearance < 60/ml/min (HR 1.032).

Overall Survival favours the ixazomib regimen (median OS not reached in either arm; HR=0.900; 95% CI: 0.615, 1.316).

The ixazomib regimen delayed the time to disease progression by approximately 6 months (median TTP 21.4 months in the ixazomib arm vs 15.7 months in the placebo arm; HR=0.712; CI 0.556, 0.912; p=0.007).

Response to treatment was reported with statistically significant difference in favour of ixazomib regimen, including overall response rate CR+PR (OR= 1.44 (1.03, 2.03), p=0.035), CR+VGPR (OR= 1.45 (1.08, 1.95), p=0.014) and CR (OR= 1.87 (1.10, 3.16), p=0.019).

Duration of response to treatment is longer with ixazomib regimen with median DOR 20.5 months ixazomib (16.62, NE) vs 15.0 m placebo (11.99, NE).

Additionally, the supportive data from the China Continuation Study provided a statistical and clinically significant effect in terms of PFS (HR=0.598; P=0.035).

Uncertainty in the knowledge about the beneficial effects

Updated efficacy data from a second interim analysis representing the most up-to date data, showed a reduced difference in effect between arms in the overall ITT population for PFS, response rates and time to progression compared to previous analysis. The hazard ratio (95% CI) for the updated PFS analysis was 0.818 (0.67, 1.0) compared to 0.742 (0.587, 0.939) as seen previously.

Although higher effects were observed in the subgroup of patients with at least 2 prior therapies, this observation is not supported by appropriate adjustments for multiplicity and lacks convincing biological and clinical plausibility.

Based on the above, and taking into account this this is an application based on a single pivotal study, there is some uncertainty about the magnitude of the trestment effect. To further support the results obtained in the pivotal trial, the Applicant will submit the final CSR for the following studies: study C16010 China Continuation a phase 3, randomized, double-blind, multicenter study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or Refractory MM, study C16014 a phase 3, randomized, double-blind, multicenter study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed MM and study C16019 a phase 3, randomized, placebo-controlled, double-blind study of oral ixazomib maintenance therapy in patients with MM following autologous stem cell transplant.

In addition, the Applicant will submit the results from NSMM-5001 study, a global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in MM patients, which will also contribute to comprenehive efficacy data.

In the pivotal trial, the median OS is not evaluable yet and the data is considered immature in this respect. The efficacy evaluation is primarily based on assessment of progression free survival and requires verification of the effect on overall survival. Therefore the CHMP considers that further overall survival analysis with longer follow up is needed from the study C16010 in order to confirm the favourable trend in OS with ixazomib regimen. The provision of these data is being proposed to be

imposed as a post-auhtorisation efficacy study in accordance with Article 1(2)(a) of Commission Delegated Regulation (EU) No 357/2014 (see Annex II to the CHMP Opinion).

Risks

The most frequently reported adverse reactions (≥ 20%) across 360 patients treated each within the ixazomib and placebo regimens in the pivotal clinical trial were diarrhoea (45% vs. 39%), constipation (35% vs. 26%), thrombocytopenia (24% vs. 11%), peripheral neuropathy (28% vs. 21%), nausea (29% vs. 22%), peripheral oedema (28% vs. 20%), vomiting (23% vs. 12%), and back pain (24% vs. 17%).

Thrombocytopaenia is reported in 20% of patients receiving the Ixazomib regimen (vs 10% placebo) with the difference between the two regimens across all grades, including Grade 3/4 (17% ixazomib and 8% placebo). All grades of bleeding [18% ixazomib and 16% placebo], Grade 3 or higher bleeding [2% ixazomib and <1% placebo], and need for platelet transfusions [6% ixazomib and 5% placebo] were reported. Thrombocytopaenia with ixazomib regimen has a nadir at day 14-21 of the treatment cycle, is predictable, reversible and manageable with supportive care and platelet transfusion.

There is an increase in gastrointestinal toxicity with ixazomib regimen compared to placebo regimen (74% vs 68%), specifically for diarrhoea (45% vs 39%), nausea (29% vs 22%) and vomiting (24% vs 11%). The majority of events were of low grade and diarrhoea was the only AE that occurred as a grade 3 in at least 5% of patients with Ixazomib (6% ixazomib vs 3% placebo). No grade 4 events were reported. Nausea or vomiting did not result in drug discontinuation while diarrhoea led to treatment discontinuation (1 or more agents in combination) in 5 patients in ixazomib regimen (vs 3 patients in placebo). The gastrointestinal toxicity is managed and some events may be prevented with supportive care (e. g. antiemetics).

The incidence of peripheral neuropathy was 28% in the ixazomib regimen and 21% in the placebo mostly of Grade 1 or 2. The most commonly peripheral neuropathy reported was sensory. Both regimens had a 2% incidence of Grade 3 peripheral neuropathy events and no grade 4 events were reported. Discontinuations of ≥1 of the agents in the study drug regimen were infrequent (1% in each regimen).

Overall, the ixazomib has significantly lower toxicity and more favourable safety profile that is superior to that of the available alternatives in this indication.

Uncertainty in the knowledge about the unfavourable effects

There are no important uncertainties in the knowledge of unfavourable effects.

Effects table

Table 59. Effects Table for Ninlaro (ixazomib) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy (data cut-off:30 October 2014 (1st IA) and 12 July 2015 (2nd IA)

Effect [1]	Short Description	Unit	Treatment	Control	Uncertainties/ Strength evidence	References
Favourable Effects						
PFS	Median 95% CI	months	20.6 (17.02, NE)	14.7 (12.91, 17.58)	some uncertainty about the magnitude of the treatment effect	Discussion on clinical efficacy (CHMP AR)
	HR 0.742 (0.587, 0.939) p=0.012					
OS 2nd IA	Median		NE	NE	Immature data	
	HR 0.868 (0.642, 1.175) p=0.359					
	HR 0.82 (p=0.055)					
ORR 2nd IA	% P= 0.089		78.6	73.2		
DOR	Median	months	26	21.7		
TTP	Median	months	22.4	17.6		
Unfavourable Effects						
Thrombocytopaenia	Incidence	%	24	11	No uncertainties	Discussion on clinical safety (CHMP AR)
Nausea	Incidence	%	29	22		
Vomiting	Incidence	%	23	12		
Diarrhoea	Incidence	%	45	39		
Constipation	Incidence	%	35	26		

Abbreviations: AE: adverse event, AR: Assessment Report, CI: confidence interval, CR: complete response, DOR: duration of response, HR: Hazard Ratio, IA: interim Analysis, KM: Kaplan Meier, NE: Not estimated, ORR: overall response rate, OS: overall survival, PFS: progression free survival, TTP: time to progression.

Benefit-risk balance

Importance of favourable and unfavourable effects

The gain in PFS of 5.9 months observed with ixazomib regoimen was considered clinically meaningful and significant, especially as it showed a consistent benefit, across subgroups, and other endpoints.

The incidence of grade 3 or higher adverse events was similar across treatment groups (76% v. 77% for placebo and ixazomib, respectively); the incidence of drug-related serious adverse events was similar across treatment groups (29% v. 28% for placebo and ixazomib, respectively); and there was no detriment in health-related quality of life based on EORTC-QLQ-C30.

Benefit-risk balance

The delay in disease progression observed with ixazomib is clinically relevant. Concerning the possible uncertainty about the magnitude of the effect, this uncertainty seems acceptable given the favourable toxicity profile, and considering that ixazomib is the first agent to allow oral triple combination therapy in this patient population, which represents a therapeutic innovation in terms of convenience for patients. Therefore, the benefit risk for ixazomib in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy is considered positive, albeit the efficacy evidence is not as comprehensive as normally required.

Discussion on the benefit-risk balance

Ixazomib an oral, highly selective and reversible proteasome inhibitor has shown a delay in disease progression in patients who received at least one prior therapy. Given the uncertainties about the true magnitude of effects, the CHMP, on the basis of Article 3(2) of Commission Regulation (EC) No 507/2006, and following a consultation with the applicant, proposed to grant a conditional marketing authorisation.

The CHMP considered that NINLARO falls within the scope of Commission Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and is designated as an orphan medicinal product.

Furthermore, the CHMP considers that requirements listed in Article 4 of Commission Regulation (EC) No 507/2006 are fulfilled on the basis of the following reasons:

a) The benefit/risk balance of the product is positive.

The 5.9 months gain in PFS data observed in the pivotal trial C16010 is significant and clinically relevant in adult patients with multiple myeloma who have received at least one prior therapy despite the uncertainty about the magnitude of the effect.

Together with the low toxicity of ixazomib and the benefit of the oral dosing regimen, the benefit-risk balance is considered positive.

b) It is likely that the applicant will be able to provide comprehensive data

The applicant will provide further comprehensive clinical data to confirm efficacy and safety of ixazomib in the proposed indication. More specifically the Applicant will provide:

- Study C16010 China Continuation a phase 3, randomized, double-blind, multicenter study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with relapsed and/or Refractory MM

- Study C16014 a phase 3, randomized, double-blind, multicenter study comparing oral ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed MM

- Study C16019 a phase 3, randomized, placebo-controlled, double-blind study of oral ixazomib maintenance therapy in patients with MM following autologous stem cell transplant.

-Study NSMM-5001 a global, prospective, non-interventional, observational study of presentation, treatment patterns, and outcomes in MM patients.

The combination of Studies C16014 and C16019 covers the entire spectrum of patients with newly diagnosed multiple myeloma (NDMM) (non-SCT and SCT). Study C16014 investigates the same treatment regimen of IRd vs placebo-Rd in NDMM not eligible for SCT and the Study C16019 investigates the effect of single agent ixazomib vs placebo as maintenance therapy in NDMM post-SCT. This data will provide compelling evidence of the extent of efficacy of ixazomib across the spectrum of patients with NDMM and will provide a data bridge to address the uncertainty about the treatment effect in patients with 1 prior therapy, since it will complement the evidence in the subgroup of 2-3 prior therapies with NDMM data and will also address the uncertainty around the consistency of treatment effect across different treatment lines.

The China Continuation study will provide additional confirmation of treatment benefit in RRMM. Data from an observational clinical study (NSMM-5001) will describe treatment patterns and patient outcomes such as response rates and time to next therapy in RRMM patients including patients treated with ixazomib and will complement the current evidence on efficacy in RRMM.

The overall data to be accumulated in various subgroups of multiple myeloma patients is regarded sufficient to provide comprehensive evidence of efficacy, including in patients who have received at least one prior therapy.

The above studies are ongoing and therefore do not raise concerns on their feasibility. Data is expected to be provided by the applicant for the China Continuation study by December 2016, for the study C16014 by December 2017, for the study C16019 by December 2018 and for study NSMM-5001 by December 2019 (see Annex II).

c) The product fulfils an unmet medical need.

Ixazomib fulfils an unmet medical need for patients with multiple myeloma who received at least one prior therapy and have limited treatment alternatives.

The efficacy benefit of the ixazomib is comparable with other therapies, but due to the significantly lower toxicity and the additional benefits of an oral dosing regimen, this product provides a major therapeutic advantage in comparison with available treatments and an important contribution to the care of patients with MM. The oral delivery of the ixazomib+LenDex regimen addresses multiple myeloma patient needs and overcome some of the significant burdens they face with currently available intravenous/injectable therapies.

d) The benefits to the public health of the immediate availability of the product outweigh the risks inherent in the fact that additional data are still required

Considering that ixazomib has favourable safety profile that is superior to that of the available alternatives, and that it is the first agent to allow oral therapy in this patient population (considerably improving convenience for patients), the immediate availability of Ninalro on the market outweighs the risk inherent in the fact that additional data are still required.

7. Recommendations following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk balance of Ninlaro in the following indication:

''NINLARO in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy''

was favourable and that the application satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation.

Divergent positions to the majority recommendation are appended to this report.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Other conditions or restrictions regarding supply and use

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
Post-authorisation efficacy study (PAES) C16010: To provide an interim report of overall survival at the time of the 3rd interim analysis and to provide a final report for the final analysis of OS from the phase 3, randomized, double-blind study C16010 in adult patients with relapsed and/or refractory multiple myeloma.	December 2019

- **Specific obligation to complete post-authorisation measures for the conditional marketing authorisation**

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
C16010 China Continuation Study: In order to further investigate the efficacy the MAH should conduct a phase 3, randomized, double-blind, multicenter study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide in patients with relapsed and/or refractory multiple myeloma and provide the final report containing the final OS analysis results.	December 2016
C16014: In order to further investigate the efficacy the MAH should conduct a phase 3, randomized, double-blind, multicenter study comparing ixazomib plus lenalidomide and dexamethasone versus placebo plus lenalidomide and dexamethasone in adult patients with newly diagnosed multiple myeloma not eligible for stem cell transplantation (SCT) and provide the final report for primary endpoint PFS.	December 2017
C16019: In order to further investigate the efficacy the MAH should conduct a phase 3, randomized, placebo-controlled, double-blind study ixazomib in maintenance therapy in patients with multiple myeloma following SCT and provide the final report for primary endpoint PFS.	December 2018
NSMM-5001: The MAH should conduct a global, prospective, non-interventional, observational study in multiple myeloma patients and provide a report of descriptive data on 1000 patients including 200 RRMM patients treated with ixazomib.	December 2019

New Active Substance Status

In light of the re-examination opinion, CHMP considers that ixazomib is a new active substance. The applicant has demonstrated that it is chemically distinct and neither it, nor its derivatives and salts, have ever been active substances in products authorised in the EEA.

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Divergent position

This application is based on a single pivotal study (C16010). In the initial analysis provided by the applicant, covering 262 progression events (from a total of 722 patients), a statistically significant prolongation of PFS (p=0.012) was seen in the overall patient population (hazard ratio point estimate 0.742, 95% CI 0.59, 0.94). OS was too immature to draw conclusions. In a more mature set of data (at a second planned analysis covering 365 progression events i.e. PFS in 50% of patients) submitted later in the procedure, the results were less convincing with a borderline statistical significance (hazard ratio point estimate 0.82; 95% CI 0.67, 1.00; p= 0.054). OS data were still immature. Although the first analysis had been defined *a priori* as primary, the second analysis provides enhanced information for quantification of the treatment effect. The level of statistical significance in both the initial analysis and the more mature analysis fell short of the usual requirement for a single pivotal trial, where the data are expected to be exceptionally compelling. Furthermore the data lacked internal consistency within the single pivotal trial. In particular the observed treatment effect was inconsistent across important clinical subgroups, for reasons that are not understood. 60% of patients in the trial had received one prior line of treatment and in this large subgroup the point estimate for hazard ratio was 0.88 (95% CI 0.65, 1.20) in the first interim analysis and 0.99 (95% CI 0.76, 1.29) in the more mature second interim analysis. No clear scientific rationale could be provided to explain the estimated lack of efficacy in patients who had had received one prior line of treatment.

An extension study performed in China and submitted as supporting evidence of efficacy showed a prolongation of PFS, but in a population of patients that differed markedly in terms of the rate of disease progression, probably explained by different baseline characteristics and treatment options. Hence, this study brings limited support to the pivotal results and does not constitute a second pivotal study.

The level of evidence, considering that it comes from one single pivotal study of borderline statistical significance and with important internal inconsistencies, does not clearly establish a relevant benefit in the claimed indication, notwithstanding the relatively favourable safety profile and the practical advantage of being orally available.

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