CLINICAL STUDY PROTOCOL

Protocol Number: X16078

A prospective, multi-centre, single arm, phase 2 assessment of the efficacy and safety of the combination of ixazomib, thalidomide and dexamethasone (ITD) for relapsed and/or refractory multiple myeloma after 1 to 3 prior lines of therapy.

Indication:	Relapsed and/or refractory multiple myeloma
Phase:	2

Protocol History

Original	3rd of November, 2015
Version 1.1	2nd of March, 2016
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This is an investigator-initiated study. The principal investigator Professor Andrew Spencer, (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

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PROTOCOL SUMMARY

Study Title: *A prospective, multi-centre, single arm, phase 2 assessment of the efficacy and safety of the combination of ixazomib, thalidomide and dexamethasone (ITD) for relapsed and/or refractory multiple myeloma after 1 to 3 prior lines of therapy.*

Phase: 2

Number of Patients: 45

Study Objectives

Primary

- To investigate the efficacy of ITD combination therapy in relapsed/refractory multiple myeloma patients – the primary endpoint is achievement of an overall response rate (ORR) defined as complete response + very good partial response + partial response (CR + VGPR + PR)
- To investigate the safety (incidence and severity of adverse events) and tolerability (total dose and percentage of planned dose delivered in each cycle) of ITD combination therapy

Secondary

- Clinical benefit rate (CBR) defined as ORR + minimal response (MR)
- Duration of response (DOR)
- Progression free survival (PFS)
- To estimate the frequency of detection of minimal residual disease (MRD) within bone marrow aspirate samples by flow cytometry (using the Euroflow 8 colour panel) in patients assessed at suspected CR and determine its impact on PFS
- Change in global health status, as measured by the PRO instruments, EORTC QLQ-C30

Tertiary/Exploratory

- Minimal residual disease (MRD) assessment via centralised next-generation (EuroFlow) flow cytometry (MFC) and correlation with serological measures of disease burden (SPEP, FreeLite). MFC to be undertaken at suspected CR.
- Purification and storage of CD138 positive MM cells at base-line for potential exploratory biomarker studies
- Isolation of circulating DNA, RNA and MiRNA at base line, 3 and 6 months post trial commencement and at relapse for potential exploratory biomarker, MRD studies and exploratory mutational analyses baseline vs. relapse.

Overview of Study Design: A prospective, single arm, multi-centre, phase 2 trial of the addition of ixazomib to a thalidomide/dexamethasone (TD) backbone. The primary objective is to determine ORR and the safety and tolerability of the combination.
Study Population: Adult patients with relapsed/refractory multiple myeloma as per international myeloma working group (IMWG) criteria who have received 1-3 lines of previous therapy.
Duration of Study: Individual patients will remain on study until disease progression, unacceptable toxicity or consent withdrawal, whichever occurs first.

SCHEDULE OF EVENTS

Schedule of Events							
	Screening[a]	For each 28 day cycle		Day 1 of cycles 3 and 6	At serological CR	EOT[c]	Follow Up[j]
		Day 1	Day 15[b]				
Study Procedures	-28 to -1						
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Demographics	X						
Medical history	X						
MM stage at diagnosis and prior MM therapies	X						
MM diagnostic karyotype and FISH if available	X						
Symptom-directed Physical Examination	X	X					X
Neurological Assessment	X	X				X	
ECOG	X	X					
Vital Signs	X	X	X				
Pregnancy Test[d]	X	X				X	
12-lead ECG	X						
FBE	X	X	X			X	
Biochemistry	X	X	X			X	
QOL assessment[e]	X	X				X	
Health Care Utilisation	X	X				X	
Skeletal Survey[f]	X				X		
Assessment of EMD if clinically indicated[g]	X				X		
B_2M	X	X					
LDH	X	X				X	
SPEP	X	X				X	
UPEP[h]	X	X				X	

FLC	X	X				X	
CFNA[i]		X		X	X	X	
BMAT[j]	X				X	X	
New primary malignancy assessment[k]		X				X	X
AE reporting	X	X				X	X
Progression data[l]							X

Abbreviations:

CR = complete response; EOT = end of treatment; FISH = fluorescent in-situ hybridization; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; FBE = full blood examination; QOL = quality of life; EMD = extramedullary disease; B_2M = beta 2 microglobulin; LDH =lactate dehydrogenase; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; FLC = free light chain assay; CFNA = circulating free nucleic acid; BMAT = bone marrow aspirate and trephine; AE = adverse event.

[a] Screening should be conducted within 28 days of starting treatment.

[b] Day 15 evaluations only for cycles 1 to 3.

[c] Patients who discontinue the study drug regimen for disease progression must complete the end-of-treatment (EOT) visit, which should occur within 30 days (± 1 week) after the last dose of study drug and before the start of subsequent antineoplastic therapy.

[d] A serum pregnancy test will be performed for women of childbearing potential during screening, day 1 of each cycle and at EOT. The serum pregnancy test may be collected up to 3 days before dosing. The results must be available and negative before the study drug regimen is administered.

[e] QLQ-C30 = Quality of Life Questionnaire.

[f] Within 60 days of cycle 1 day 1 acceptable at screening. To be repeated at time of serological CR and otherwise only if clinically indicated.

[g] For those with documented extramedullary disease, radiographic assessments should be undertaken at screening, at the time of serological CR and otherwise, only if clinically indicated. The same imaging modality used at screening (CT/PET-CT/MRI) should be used for all follow-up assessments.

[h] Only to be repeated if abnormal at baseline.

[l] Correlative studies (peripheral blood collection)

[j] BMAT will be obtained at screening, at serological CR and progression for response assessment and correlative studies.

[k] New primary malignancies that occur during the follow-up period must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product

[l] Data collection for response, progression free survival, salvage therapy, response to salvage therapy and survival following salvage therapy (second (PFS2)), date of death

[j] Follow up will continue every 3 months until all patients remaining on study have been followed for at least 12 months

LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
5-HT_3	5-hydroxytryptamine 3 serotonin receptor
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
AUC_{inf}	area under the plasma concentration versus time curve from zero to infinity
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
BZD	benzodiazepines

Abbreviation	Term
CBC	complete blood count
CFR	code of federal regulations
CL	clearance, IV dosing
CL_P	plasma clearance
CL_{Total}	total clearance
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRM	continual reassessment method
CRP	c-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CT	computed tomography
C_{trough}	single-dose end of dosing interval (trough) concentration
CV	coefficient of variation
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	end of study (visit)

Abbreviation	Term
EOT	end of treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
Hb	hemoglobin
Hct	hematocrit
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
IB	investigator's brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
KPS	karnofsky performance status

Abbreviation	Term
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nil by mouth
NYHA	New York Heart Association
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Pgp	p-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day

Abbreviation	Term
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SmPC	summary of product characteristics
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
TMC	trial management committee
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Disease Under Investigation:

Relapsed/Refractory Multiple Myeloma (MM)

MM a common haematologic malignancy of plasma cells, is both a clinically and biologically heterogeneous disease. Since the introduction of novel agents into clinical practice, median survival of patients with MM has improved by 50%.(1) These therapies include thalidomide and a class of thalidomide derived analogues called immunomodulatory drugs (IMiDs), including lenalidomide and pomalidomide, as well as the proteosome inhibitor (PI) bortezomib. Despite the availability of these novel agents, MM remains incurable accounting for 20% of all deaths from haematologic malignancy.(2)

IMiDs including thalidomide have been shown to have efficacy in MM in all phases of the disease, both as single agents and as a component of combination therapies and have been an affordable global standard of care in myeloma for over a decade.(3) The triplet therapy cyclophosphamide, thalidomide and dexamethasone (CTD) is a standard therapy for RRMM that is affordable, well tolerated and associated with an overall response rate (ORR) in our hands of 45% with a median duration of treatment of 3 cycles (data on file). Published efficacy data for standard dose CTD is limited with a median duration of treatment of 6 months reported from a recent single study of 52 RRMM patients.(4)Therapy with bortezomib, thalidomide and dexamethasone has previously be shown to be highly effective in both NDMM and RRMM.(5, 6) There is limited data on the efficacy and tolerability of the combination of ixazomib, thalidomide and dexamethasone, however it may prove an attractive option as an oral alternative.

Scientific Background

Ixazomib (MLN9708)

1.2 Preclinical Experience

Please refer to the current ixazomib Investigator's Brochure (IB)

1.3 Clinical Experience

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapsed/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate

both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, 2 phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with Revlimid and Dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies have evaluated drug-drug interactions with ketoconazole, clarithromycin, and rifampin, as well as the effect of food, renal impairment, and hepatic impairment on the PK of ixazomib. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of RRMM are ongoing.

As of 27 March 2013, preliminary clinical data was available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with bortezomib (VELCADE) though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (as per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (as per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but (as outlined in Section 6.7) has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n = 201) irrespective of causality to ixazomib, include

nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n = 173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), peripheral edema (21%, each), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide where rash is an overlapping toxicity.

Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

1.4 Pharmacokinetics and Drug Metabolism

After oral dosing, absorption of ixazomib is rapid with a median first time to maximum observed plasma concentration (Tmax) of approximately 1 hour postdose. The plasma exposure (AUC) of ixazomib increases in a dose-proportional manner over a dose range of 0.2 to 10.6 mg based on population PK analysis. The absolute oral bioavailability (F) of ixazomib is estimated to be 58% based on population PK analysis. A high-fat meal reduced ixazomib Cmax by 69% and AUC0-216 by 28%. This indicates that a high-fat meal decreases both the rate and extent of absorption of ixazomib. Therefore, ixazomib should be dosed 2 hours after food or 1 hour before food.

The steady-state volume of distribution of ixazomib is large and is estimated to be 543 L based on the population PK model. Based on in vitro plasma protein binding measurements on samples from clinical studies (Studies C16015 and C16018), ixazomib is highly bound to plasma proteins (99%). Ixazomib concentrations are higher in whole blood than in plasma, indicating extensive partitioning of ixazomib into red blood cells, which are known to contain high concentrations of the 20S proteasome.

Metabolism appears to be the major route of elimination for ixazomib. In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450 (CYP) and non-CYP proteins. At concentrations exceeding those observed clinically (10 µM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), CYP2C19 (4.8%), and 2C9 (1%). At 0.1 and 0.5 µM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, non-CYP proteins contribute to the clearance of ixazomib and no specific CYP isozyme predominantly contributes to the clearance of

ixazomib. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected.

Ixazomib is neither a time-dependent inhibitor nor a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYPs 1A2, 2B6, and 3A4/5 activity or corresponding immunoreactive protein levels. Thus, the potential for ixazomib to produce DDIs via CYP isozyme induction or inhibition is low.

Ixazomib is not a substrate of BCRP, MRP2 and OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Ixazomib is unlikely to cause or be susceptible to clinical DDIs with substrates or inhibitors of clinically relevant drug transporters.

The geometric mean terminal half-life (t1/2) of ixazomib is 9.5 days based on population PK analysis. For both IV and oral dosing, there is an approximately average 3-fold accumulation (based on AUC) following the Day 11 dose for the twice-weekly schedule and a 2-fold accumulation (based on AUC) following the Day 15 dose for the once-weekly schedule.

Mean plasma clearance (CL) of ixazomib is 1.86 L/hr based on the results of a population PK analysis. Taken together with the blood-to-plasma AUC ratio of approximately 10, it can be inferred that ixazomib is a low clearance drug. Using the absolute oral bioavailability (F) estimate of 58% (also from the population PK model), this translates to an apparent oral plasma clearance (CL/F) of 3.21 L/hr. The geometric mean renal clearance for ixazomib is 0.119 L/hr, which is 3.7% of CL/F and 6.4% of CL estimated in the population PK analysis. Therefore, renal clearance does not meaningfully contribute to ixazomib clearance in humans. Approximately 62% of the administered radioactivity in Study C16016 was recovered in the urine and 22% of the total radioactivity was recovered in the feces after oral administration. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged ixazomib up to 168 hours after oral dosing, suggesting that most of the total radioactivity in urine was attributable to metabolites.

The PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor, and hence no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. Consistently, in a population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Based on information from the clinical rifampin DDI study, ixazomib Cmax and AUC0-last were reduced in the presence of rifampin by approximately 54% and 74%, respectively. Therefore, the co-administration of strong CYP3A inducers with ixazomib is not recommended.

Mild or moderate renal impairment (CrCL ≥ 30 mL/min) did not alter the PK of ixazomib based on the results from a population PK analysis. As a result, no dose adjustment is required for patients with mild

or moderate renal impairment. In a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or ESRD patients requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is appropriate in patients with severe renal impairment or ESRD requiring dialysis. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not readily dialyzable, consistent with its high plasma protein binding (99%).

The PK of ixazomib is similar in patients with normal hepatic function and in patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (total bilirubin <1.5 times the upper limit of normal [ULN]), based on the results from a population PK analysis. Consequently, no dose adjustment is required for patients with mild hepatic impairment. In a dedicated PK study in patients with moderate (total bilirubin >1.5 to 3 times the ULN) or severe (total bilirubin >3 times the ULN) hepatic impairment (Study C16018), unbound dose-normalized AUC0-last was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. Therefore, a reduced starting dose of ixazomib is appropriate in patients with moderate or severe hepatic impairment.

There was no statistically significant effect of age (23-91 years), gender, body surface area (1.2-2.7 m2), or race on the clearance of ixazomib based on the results from the population PK analysis.

Further details on these studies are provided in the IB.

1.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

As of 27 March 2013, a total of 507 patients with differing malignancies (MM, AL amyloidosis, nonhematologic cancers, and lymphoma) had been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
	cycle	
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W
C16010 RRMM N = 200	PO, W, with LenDex versus placebo-LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W
C16014 Symptomatic MM N=701	PO, combination with LenDex	ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22
C16015 Symptomatic MM with normal renal function or severe renal impairment N=28	PO, combination with Dex	Part A: ixazomib 3.0 mg on Day 1 Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16017 RR follicular lymphoma N=58	PO, W	4.0, 5.3, and 7.0 mg, W Treatment at RP2D once determined.
C16018 Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction N=45	Part A: PO, Day 1 of 15-day cycle Part B: PO, W	1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)
TB-MC010034 RRMM N = 10	PO, W	4.0 mg, W Single agent: 4.0 mg Combination with Rd

Abbreviations:

RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or refractory systemic light chain amyloidosis RRMM = relapsed and/or refractory multiple myeloma; TBD = to be determined; TW = twice weekly; W = weekly; RP2D= recommended phase 2 dose.

Note that blinded data from pivotal Studies C16010 and C16011 are not included.

[a] Approximate BSA and fixed dosing equivalence: 3 mg~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg~ equivalent to 2.97 mg/m^2 BSA dosing.

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with VELCADE though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

In studies C16003, C16004, C16007, and C16009 investigating single-agent oral ixazomib in patients with differing malignancies (MM, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of

201 patients had been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

	Oral Single Agent
	Total
Primary System Organ Class	**n = 201**
Preferred Term	**n (%)**
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Oedema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

Primary System Organ Class Preferred Term	Oral Single Agent Total n = 201 n (%)
Decreased appetite	64 (32)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular[a]	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnoea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

	Oral Single Agent Total n = 201 n (%)
Primary System Organ Class **Preferred Term**	

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

[a] Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

As of 27 March 2013, there were 5 studies actively enrolling patients with MM to investigate oral ixazomib in combination with standard combination regimens. The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, related is defined as related to any study drug in the combination regimen.

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Primary System Organ Class **Preferred Term**	
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Oedema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalaemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anaemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular[a]	29 (17)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 n (%)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Dyspnoea	26 (15)
Infections and infestations	92 (53)
Upper respiratory tract infection	35 (20)
Psychiatric disorders	73 (42)
Insomnia	50 (29)

Source: Ixazomib Investigator's Brochure Edition 7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

Data from ongoing blinded pivotal trials (C16010) are not included.

[a] Note that rash maculopapular and rash macular represent the 2 most common terms used to describe rash.

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors (7), non-Hodgkin's disease, Hodgkin's disease (8), relapsed and/or refractory multiple myeloma [RRMM; (9); (10)], relapsed or refractory systemic light chain amyloidosis [RRAL; (11)], and newly diagnosed multiple myeloma [NDMM; (12); (13); (14)]) to date. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of ixazomib.

1.6 Relapsed and/or Refractory Multiple Myeloma

The early development of ixazomib in patients with RRMM involved 2 studies (C16003 and C16004) with similar objectives, but each investigated 1 of the 2 dosing schedules commonly used with the first-in-class proteasome inhibitor, VELCADE. Study C16003 was an open-label, dose escalation, phase 1 study of ixazomib dosing on a twice-weekly schedule on Days 1, 4, 8, and 11 of a 21-day cycle in adult patients with RRMM.((15), (16)) Study C16004 was an open-label, dose escalation, phase 1 study of ixazomib dosing on a weekly schedule on Days 1, 8, and 15 of a 28-day cycle in adults patients with RRMM.((10), (12), (17)) Both studies have now completed enrollment. The DLTs in Study C16003 were rash macular and thrombocytopenia and the DLTs in C16004 were nausea, diarrhea, vomiting, and erythema multiforme.

In the dose escalation component of both studies, patients had MM that had relapsed following at least 2 lines of therapy that must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In both studies, when the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled into 1 of 4 expansion cohorts, including a relapsed and refractory cohort, a carfilzomib cohort, a proteasome inhibitor-naïve cohort, and a VELCADE-relapsed cohort.

Final study results are currently being analyzed, but preliminary data suggest that ixazomib has anti-tumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated. Please refer to the ixazomib IB for further information.

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

Multiple research paths are being explored in patients with NDMM with a focus on evaluating ixazomib in combination with agents commonly used across treatment settings. The development of ixazomib in combination with lenalidomide with dexamethasone (LenDex) in patients with NDMM who are transplant eligible or ineligible involves 2 studies (C16005 and C16008) with similar study designs except for a few key differences, namely the schedules of ixazomib and dexamethasone. Ixazomib is also being evaluated in combination with melphalan and prednisone (MP) for patients who are not transplant eligible due to age or coexisting morbidity (in Study C16006).

All 3 studies are phase 1/2, with phase 1 focusing on safety and phase 2 on efficacy (and further characterization of safety). Please refer to the ixazomib IB and SMA for further information.

1.8 Clinical Trial Experience Using the Intravenous Formulation of Ixazomib

See the IB for descriptions of the 2 studies that investigated IV ixazomib in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.9 Study Rationale

Despite many currently available therapeutic agents for patients with RRMM further relapses remain inevitable highlighting the requirement for newer and more effective therapeutic options. The combination of cyclophosphamide, thalidomide and dexamethasone (CTD), although shown to have some efficacy in RRMM, still has an overall response rate (ORR) of only 45% (internal retrospective review) with some toxicities seen in most patients.

Ixazomib is a next generation oral proteasome inhibitor in clinical development for the treatment of both haematologic and non-haematologic malignancies and is the first orally bioavailable proteasome inhibitor to enter clinical development. Ixazomib has been evaluated as an oral single agent in phase 1 studies in RRMM as well as in combination with standard treatments. Based on encouraging preliminary data a Phase 3 trial in RRMM (C16010) is currently evaluating ixazomib in combination with lenalidomide and dexamethasone (Rd), however, no current study is evaluating the benefit of ixazomib in combination with a thalidomide/dexamethasone (TD) backbone in RRMM patients.(18)

Therefore the purpose of this study is to determine the safety, tolerability and efficacy of oral ixazomib when added to a TD backbone at standard doses.

1.10 Potential Risks and Benefits

Please refer to the current ixazomib IB, prescribing information for thalidomide (Australian product label) and prescribing information for dexamethasone (Australian product label)

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Millennium. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports expanded development of ixazomib for the treatment of patients with advanced malignancy.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives are to investigate the:

- Efficacy
- Safety and tolerability

of combination therapy with ixazomib, thalidomide and dexamethasone (ITD) in patients with relapsed/refractory multiple myeloma.

2.2 Secondary Objectives

The secondary objectives are to investigate:

- Clinical benefit rate (CBR) defined as ORR + minimal response (MR)
- Duration of response (DOR)
- Progression free survival (PFS)
- To estimate the frequency of detection of minimal residual disease (MRD) within bone marrow aspirate samples by flow cytometry (using the Euroflow 8 colour panel) in patients assessed at suspected CR and determine its impact on PFS
- Change in global health status, as measured by the PRO instruments, EORTC QLQ-C30

2.3 Tertiary/Exploratory Objectives

- Minimal residual disease (MRD) assessment via centralised multi-parameter flow cytometry (MFC) and correlation with serological measures of disease burden (SPEP, FreeLite). MFC to be undertaken at suspected CR.
- Purification and storage of CD138 positive MM cells at base-line for potential exploratory

biomarker studies

- Isolation of circulating DNA, RNA and MiRNA at base-line, at 3 and 6 months post trial commencement and at relapse for potential exploratory biomarker and MRD studies and exploratory mutational analyses baseline vs. relapse e.g. utilising RNA Seq

3. STUDY ENDPOINTS

3.1 Primary Endpoints

The primary efficacy endpoint is the achievement of an overall response (sCR + CR + VGPR + PR + MR) as defined by International Myeloma Working Group (IMWG) criteria while on ITD combination therapy.

The co-primary safety endpoints are the incidence and severity of adverse events while on ITD therapy and the tolerability endpoints are total dose and percentage of planned dose of each study drug delivered in each cycle.

3.2 Secondary Endpoints

The secondary endpoints include:

- Duration of response (DOR)
- Progression free survival (PFS)
- MRD negativity
- Global health status, as measured by the PRO instruments, EORTC QLQ-C30.

3.3 Tertiary/Exploratory Endpoints (*if applicable)*

The exploratory endpoints include:

- Minimal residual disease (MRD) via centralised multi-parameter flow cytometry (MFC) and correlation with serological measures of disease burden (SPEP, FreeLite). MFC to be undertaken at suspected CR.
- Purification and storage of CD138 positive MM cells at base-line for potential exploratory biomarker studies

- Isolation of circulating DNA, RNA and MiRNA at base-line, at 6 and 12 months post trial commencement and at relapse for potential exploratory biomarker and MRD studies and exploratory mutational analyses baseline vs. relapse e.g. utilising RNA Seq

4. STUDY DESIGN

4.1 Overview of Study Design

Single arm, multi-centre phase 2 trial of the combination of ixazomib with a thalidomide/dexamethasone backbone.

Treatment is with ixazomib 4mg on day 1, 8, 15 plus thalidomide 100mg daily and dexamethasone 40mg once weekly until disease progression, unacceptable toxicity or withdrawal of patient consent, whichever occurs first.

Drug	**Dose**	**Schedule (1 cycle = 28 days)**
Ixazomib	4mg	Days 1, 8 and 15 of 28 day cycle
Thalidomide	100mg	Days 1-28 of 28 day cycle
Dexamethasone	40mg	Days 1, 8, 15, 22 of 28 day cycle

4.2 Number of Patients

In total 45 patients are planned to be enrolled.

4.3 Duration of Study

It is estimated that recruitment will take 12 months.

- Based on previous experience in the MM14 trial (a prospective randomised phase 2 study of single agent pomalidomide maintenance versus combination pomalidomide and low dose dexamethasone maintenance following induction with the combination of pomalidomide and low dose dexamethasone in patients with relapsed and refractory

myeloma previously treated with lenalidomide) where 13 patients were recruited in a similar population within 6 months in a single centre it is reasonable to consider that recruitment of 45 patients at multiple sites within 12 months is feasible.

Number of months from Takeda approval to site activation of study: 3
Number of months from study activation to first patient in (FPI): 3
Number of months from last patient in (LPI) to last patient out (LPO): 24
Number of months from LPO to Final data/Manuscript: 6

It is estimated that the average number of cycles per patient will be 4. Patients will continue on protocol treatment (combination therapy) until any of the following occurs:
- Unacceptable toxicity/adverse event that may cause severe or permanent harm which rule out continuation of the study drug
- Relapse/progressive disease (as defined by IMWG – Appendix 3)
- Consent withdrawal
- Major violation of the study protocol
- Suspected pregnancy
- Death

Following cessation of ITD therapy patients will remain on trial for a follow up phase to document progression free survival, salvage therapy, response to salvage therapy and survival following salvage therapy (PFS2, second PFS), date of death. Follow up will continue until all patients remaining on study have been followed for at least 12 months.

The trial may also be terminated early by the TMC if safety concerns emerge with this treatment.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.

2. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Female patients who:

   - Are postmenopausal for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR
   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, OR
   - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:

   - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
   - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

4. Patients must have a diagnosis of a relapsed/refractory multiple myeloma and have had between 1-3 prior therapies

5. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 (See appendix 11.1).

6. Patients must meet the following clinical laboratory criteria:

   - Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3 and platelet count $\geq$ 75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.
   - Total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 3 \times$ ULN.
   - Calculated creatinine clearance $\geq$ 30 mL/min (see Appendix 11.3).

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Patients with known thalidomide refractory disease or thalidomide intolerance.

2. Female patients who are lactating or have a positive serum pregnancy test during the screening period.

3. Failure to have fully recovered (ie, $\leq$ Grade 1 toxicity) from the reversible effects of prior chemotherapy.

4. Major surgery within 14 days before enrollment.

5. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the combination of ixazomib, thalidomide and dexamethasone.

6. Central nervous system involvement with the disease under study (multiple myeloma).

7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

8. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure , unstable angina, or myocardial infarction within the past 6 months.

9. Systemic treatment, within 14 days before the first dose of ixazomib, with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

10. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

11. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

12. Known allergy/intolerance to any of the study medications, their analogues, or excipients in the various formulations of any agent.

13. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib, thalidomide and/or dexamethasone including difficulty swallowing.

14. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

15. Patient has $\geq$ Grade 2 peripheral neuropathy, or Grade 1 with pain on clinical examination during the screening period.

16. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

17. Patients that have previously been treated with ixazomib, or participated in a study with ixazomib whether treated with ixazomib or not.

18. Patients who are either contraindicated or unwilling to receive anticoagulation therapy.

19. Patients who are either contraindicated or unwilling to receive anti-viral prophylaxis for prevention of Varicella reactivation.

20. Patients that do not agree to be registered in, and abide by the requirements of the i-access® Risk Management Program

6. STUDY DRUG

6.1 Description of Investigational Agents

Ixazomib Capsules

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink

For additional details, please see the ixazomib IB.

6.2 Study Drug Administration

Ixazomib Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see Section 6.3).

Capsules of ixazomib will be supplied by Millennium as capsules of 2.3-, 3.0- and 4.0 mg ixazomib.

The prescribed administration of ixazomib doses in this study is 4mg ixazomib in a 28 day cycle.

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Ixazomib should be taken on an empty stomach (no food or drink) at least 1 hour

before or at least 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

Ixazomib Destruction

Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

Standard of Care Therapies

6.2.2 Thalidomide Administration

Thalidomide will be provided as a standard of care therapy via the PBS. Therefore all patients will need to be registered in, and abide by, the requirements of the i-access® Risk Management Program. Thalidomide will be given as a single, daily oral dose of 100mg for 28 days out of the 28-day cycle. No dose reduction with be made for impaired creatinine clearance. Administration of thalidomide will be approximately the same time each day. Patients should be instructed to swallow thalidomide capsules whole with or without food and not to break, chew, or open the capsules. If a dose of thalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of thalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

6.2.3 Dexamethasone Administration

Dexamethasone will be given as an oral dose of 40 mg/day weekly on Days 1, 8, 15, and 22 of a 28-day cycle.

Dexamethasone should be taken at approximately the same time preferably with food/milk to avoid stomach irritation. If a dose of dexamethasone is missed, the dose should be taken as soon as the patient remembers it. If enough time has elapsed that it is almost time for the next dose (within 72 hours), the missed dose should be skipped and the next dose taken according to the regular dosing

schedule. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

All patients should receive acid reflux prophylaxis (ie pantoprazole 40mg daily) as per institutional protocol

6.2.4 Thromboembolic prophylaxis as per institutional protocol

Clinical studies with thalidomide in combination with dexamethasone as well as other chemotherapeutic agents have shown an increase in risk of VTE. Aspirin or LMWH has been reported to be effective in reducing the incidence of DVT in myeloma patients treated with thalidomide.

For this study, all patients will receive anti-thrombotic prophylaxis, either aspirin 100mg daily or prophylactic doses of LMWH according to hospital guidelines or physician preference. All patients will be monitored for signs and symptoms of VTE while on study treatment. Those patients in whom anti-thrombotic prophylaxis is contraindicated (or refused by the patient) will by excluded from the study.

6.2.5 Anti-viral prophylaxis as per institutional protocol

All patients should be commenced on anti-viral prophylaxis for the prevention of reactivation of herpes at the study commencement (i.e. on or before cycle 1 day 1).

6.2.6 Bisphosphanate prophylaxis as per institutional protocol

Bisphosphonate prophylaxis for bone protection (ie zolendronic acid 4mg iv monthly) is recommended as per institutional protocol.

6.3 Dose-Modification Guidelines

Causality of adverse events will be assigned by the treating clinician at the time of occurrence and dose-modifications undertaken accordingly. Where there is an overlap of toxicity profile, dose reduction of offending agent as determined by the treating clinician will be undertaken. For example; myelosuppression (haematological AE) would result in dose reduction of ixazomib in the first instance, whereas peripheral neuropathy would result in dose reduction of thalidomide initially.

6.3.1 Recommended Ixazomib, Thalidomide and Dexamethasone Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

Treatment with the combination of ixazomib/thalidomide/dexamethasone will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 75,000/mm^3.
- All treatment-related non-hematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition except for isolated gamma glutamyl transferase (GGT) elevations.

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Principal Investigator.

For dosing recommendations upon recovery, refer to Table 6-2 and Table 6-3.

Table 6-1 Ixazomib Dose Adjustments

Dose Level	Dose (mg)
Starting Dose	4.0 mg
-1	3.0 mg
-2	2.3 mg
-3	Discontinue

Note: If ixazomib is discontinued patients may continue thalidomide and dexamethasone and therefore remain on study.

Dosage adjustments for hematologic toxicity are outlined in Table 6-2.

Table 6-2 I**xazomib and Thalidomide** Dose Adjustments for Hematologic Toxicities

Criteria	Action
<u>Within-Cycle Dose Modifications</u>	
• If platelet count $\leq 30 \times 10^9$/L, ANC $\leq 0.50 \times 10^9$/L on any dosing day other than Day 1). • ANC $\leq 1.0 \times 10^9$/L with fever at any time during a cycle.	Ixazomib, thalidomide and dexamethasone dose should be withheld. Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values (see Section 6.3.1) on at least 2 occasions. Or at physician's discretion if G-CSF is used for neutropenia. Upon recovery ixazomib be reinitiated with 1 dose level reduction. During the 2nd observation of thrombocytopenia, thalidomide should be reinitiated at 1 dose level reduction, and continue alternating dose reductions whilst the patient is on treatment
<u>Dose Modifications for Subsequent Treatment Cycles</u>	
• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined in Section 6.3.1: as follow: ANC $< 1.0 \times 10^9$/L, platelet count $< 75 \times 10^9$/L, or other nonhematologic toxicities > Grade 1 or not to the patient's baseline condition	Hold ixazomib and thalidomide until resolution as per criteria Section 6.3.1. Upon recovery thalidomide should be reinitiated with 1 dose level reduction (if ixazomib was already reduced during the preceding cycle. Continue alternating dose reductions whilst the patient is on treatment. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the PI.

Treatment modifications due to ixazomib and/or thalidomide-related AEs are outlined in Table 6-3.

Table 6-3 **Ixazomib/Thalidomide** Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Ixazomib and Thalidomide	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy without pain	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only (19)
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold ixazomib and thalidomide until resolution to Grade ≤ 1 without pain or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) (19)
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold ixazomib and thalidomide until resolution to Grade ≤ 1 or baseline • Reduce thalidomide to next lower dose upon recovery. • During the 2nd observation of new or worsening Grade 2 peripheral neuropathy with pain or Grade 3, ixazomib should be reinitiated at 1 dose level reduction, and continue alternating dose reductions whilst the patient is on	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated (19)

Table 6-3 **Ixazomib/Thalidomide** Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Ixazomib and Thalidomide	Further Considerations
New or worsening Grade 4 peripheral neuropathy	• Discontinue ixazomib and thalidomide • Dexamethasone therapy may be continued	
Grade 2 Rash	• Symptomatic recommendations as per section 6.7	The investigator may consider dose modifications and symptom management.
Grade 3 nonhematologic toxicity judged to be related to Ixazomib and/or thalidomide (including Grade 3 rash)	• Hold ixazomib and thalidomide (and dexamethasone if thought by clinician to be a possible causative agent) until resolution to Grade $\leq$ 1 or patient's baseline • Reduce implicated study drug (ixazomib, thalidomide or dexamethasone) to next lower dose upon return to $\leq$ Grade 1 or patient's baseline (investigator discretion, consider dose reduction if delay of >2 weeks to recovery to these values).	Symptomatic recommendations noted in Section 6.7

Table 6-3 **Ixazomib/Thalidomide** Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Ixazomib and Thalidomide	Further Considerations
Subsequent recurrence Grade 3 nonhematologic toxicity	• Hold study drugs (ixazomib, thalidomide and dexamethasone) until resolution to Grade 1 or patient's baseline • Reduce implicated study drug (ixazomib, thalidomide or dexamethasone) to next lower dose (investigator discretion, consider dose reduction if delay of >2 weeks to recovery to these values).	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 nonhematologic toxicities judged to be related to ixazomib and/or thalidomide	• Consider permanently discontinuing ixazomib and/or thalidomide	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

Once any study drug/s is/are reduced for any toxicity, the dose may not be re-escalated. If any of ixazomib, thalidomide or dexamethasone is discontinued permanently patients may remain on study with the remaining agent/s.

For other side effects (ie constipation) symptomatic management (aperients etc.) should be attempted prior to a dose reduction.

6.3.2 Recommended Dose Modifications for Thalidomide Treatment Associated Toxicity

Dosage adjustments for thalidomide are outlined in Table 6-4. Treatment modifications due to thalidomide-related AEs are outlined in Table 6-5.

Table 6-4 Thalidomide Treatment Modifications

Dose level	**Daily, days 1-28 of 28 day cycle**
Starting dose	100mg
-1	50mg
-2	Discontinue

For other side effects attributed to thalidomide (ie constipation) symptomatic management (aperients etc.) should be attempted prior to a dose reduction

Recommended Dose Modifications for Dexamethasone Treatment Associated Toxicity

Dosage adjustments for dexamethasone are outlined in Table 6-6

Table 6-5 Dexamethasone Treatment Modifications

Dose level	**Weekly, days 1, 8, 15, 22 of 28 day cycle**
Starting dose	40mg
-1	20mg
-2	8mg
-3	4mg
-4	Discontinue

Dose reduction of dexamethasone to a minimum of 4mg weekly will be allowed to manage toxicities. Dexamethasone should be discontinued if patient is unable to tolerate 4mg dose. Patients intolerant of dexamethasone 4mg weekly can continue on ixazomib and thalidomide therapy.

6.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: If there were to be a drug-drug interaction with an inducer, ixazomib exposure would be decreased:

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

The following medicinal products and procedures are prohibited during the study.

- Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba

- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression)
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day.

6.5 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IVF should be given to prevent volume depletion.
- Growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.6 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

Thalidomide has caused severe birth defects when taken during pregnancy. Thalidomide should never be used by women who are pregnant or who could become pregnant whilst taking the medicine or could become pregnant within 4 weeks after stopping the medicine. Even a single dose can cause birth defects.(20) It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus.

Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.7 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Management guidelines regarding these events are outlined below. Further details of management of ixazomib AEs are described in Section 6 of the ixazomib IB.

Prophylaxis Against Risk of Reactivation of Herpes Infection

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Antiviral prophylaxis such as acyclovir, valacyclovir, or other antivirals should be initiated in all patients (Section 6.2.5).

Nausea and/or Vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of study drug and during treatment.

Diarrhea

Prophylactic anti-diarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

Erythematous Rash With or Without Pruritus

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of

ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body or oral or topical antihistamines). A rare risk is Stevens-Johnson Syndrome, a severe and potentially life-threatening rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice. Punch biopsies for histopathological analysis are encouraged at the discretion of the investigator.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 6-2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

Fluid Deficit

Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration.

Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with ixazomib. This condition is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Diagnosis may be confirmed by magnetic resonance imaging (MRI). If the syndrome is diagnosed or suspected, symptom-directed treatment should be maintained until the condition is reversed by control of hypertension or other instigating factors.

Transverse Myelitis

Transverse myelitis has also been reported with ixazomib. It is not known if ixazomib causes transverse myelitis; however, because it happened to a patient receiving ixazomib, the possibility that ixazomib may have contributed to transverse myelitis cannot be excluded.

6.8 Preparation, Reconstitution, and Dispensing

Ixazomib and thalidomide are anticancer drugs and as with other potentially toxic compounds caution should be exercised when handling ixazomib or thalidomide capsules/tablets.

6.9 Packaging and Labeling

The study drug ixazomib capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

The capsules are individually packaged using cold-form foil-foil blisters that are in a child-resistant carton. There are 3 capsules in each wallet/carton.

Thalidomide and dexamethasone will be commercially obtained and all packaging and labeling procedures should be adhered to.

6.10 Storage, Handling, and Accountability

Upon receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because ixazomib is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules.

Thalidomide and dexamethasone will be supplied by the site via the pharmaceutical benefits scheme (PBS) from commercial sources and must be stored according to the instructions provided in the manufacturer's package insert.

6.11 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

6.12 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Suspected pregnancy
- Lost to follow-up
- Progressive disease
- Study terminated
- Other

Patients who are withdrawn from the study will not be replaced.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

7. STATISTICAL AND QUANTITATIVE ANALYSES

7.1 Statistical Methods

The primary efficacy and safety analyses will be conducted after all patients, who are still receiving ITD combination therapy have completed 4 cycles of therapy. The additional data for patients continuing to

receive study treatment beyond this time, as allowed by the protocol, will be summarized in a final report once all patients remaining on study have completed 1 year of follow-up.
The primary efficacy analysis will be an intention-to-treat analysis conducted on the Full Analysis Set (FAS) which comprises all patients registered on the study. A sensitivity analysis of the primary efficacy endpoint will also be conducted on the Per-Protocol Set (PPS) which consists of a subset of patients in the FAS who have been compliant with the requirements of the protocol, i.e. patients without a major protocol deviation. Major protocol deviations include, but are not limited to, incomplete documentation of response status at registration, a response status of MR or better at registration, and, other anti-neoplastic therapy administered after registration on the study. Major protocol deviations will be documented, and the PPS will be determined, prior to locking the database for the primary efficacy analysis. The primary safety analysis will be conducted on the Safety Set which consists of the subset of patients in the FAS who received at least one dose of ixazomib.

Demographic and other baseline data collected at registration will be summarized descriptively for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, means, standard deviations, medians, 25th and 75th percentiles, minima and maxima will be presented.

7.1.1 Determination of Sample Size

The primary efficacy analysis will be based on the calculation of the observed overall response rate (ORR) and its posterior probability distribution. An observed ORR of 60% is considered to be clinically important while a true ORR of 45% or less is considered to be too low to merit adoption of ITD combination therapy.
Evidence of efficacy of ITD combination therapy might be reasonably concluded if the observed ORR is ≥ 60% (i.e. a clinically important result is observed) and there is ≥ 90% posterior probability that the true ORR is > 45% (i.e. a sufficiently high level of proof that the true ORR is not lower than the historical rate (internal review)).
The justification of the sample size is accordingly based on this Bayesian approach to “proof of concept” (PoC) in phase II trials ((21)).
A minimally informative prior distribution for the true ORR with a median equal to the clinical threshold for futility (45%) will be used, namely the Beta distribution (Beta(a, b)) where a=ln(0.5)/ln(0.45) = 0.86805 and b=1. This prior distribution is equivalent to assuming we have prior information on approximately 1.87 patients. The posterior probability for an ORR > 45% given “x” overall responses out of “n” patients is given by the right tail (from p=0.45 to p=1.0) of the Beta(a+x, b + n – x) distribution.

For n=45 and a true ORR of 65%, the probability of declaring efficacy, based on this approach, is 0.80. Accordingly, provision is being made to register 45 patients on the trial. When we observe a rate of 60% or more (i.e. when the first PoC criterion is met) the posterior probability, that the true ORR is > 45%, is 90% when the observed rate is based on at least 20 patients (in which case the second PoC criterion is

automatically met) and 95% when the observed rate is based on at least 31 patients. Consequently, if accrual is slow and the trial is terminated early for this reason, there is still scope to demonstrate PoC.

7.1.2 Randomization and Stratification -Not applicable

7.1.3 Populations for Analysis

Data from all patients registered on the study, the FAS, will be collected and, following the intention to treat principle, the analysis of efficacy will be based on the FAS. Analysis of safety and tolerability will be based on the Safety Set – the subset of patients in the FAS who received at least one dose of ixazomib.

7.1.4 Procedures for Handling Missing, Unused, and Spurious Data

Patients without re-staging information for any reason and who are not known to have achieved at least a PR while on ITD therapy will be deemed to have not met the primary efficacy endpoint. Time to event data will be censored at the study censor date (see below) except for patients deemed lost to follow-up – their time to event data will be censored at the earlier of the study censor date and the date of last assessment. Missing quality of life data will, in linear mixed model analyses, be assumed to be missing at random, but if the missingness is due to death or withdrawal from the study due to unacceptable toxicity or progression, the missing measures will be imputed and the patient deemed to have "zero" global quality of life from the date of withdrawal from the study.

7.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics such as gender, age, race, weight, height, BSA, primary diagnosis, and other parameters will be summarized descriptively for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, means, standard deviations, medians, 25th and 75th percentiles, minima and maxima will be presented.

7.1.6 Efficacy Analysis

The primary efficacy objective is to determine the overall response rate to treatment with ITD combination therapy in RRMM patients. Overall response is defined as achievement of a PR or better

(PR, VGPR, CR or sCR) as defined by the IMWG criteria (Appendix 4). The overall response rate (ORR) will be calculated as the number of patients who have experienced at least a partial response, divided by the number of patients registered on the trial. Patients who withdraw from the study prior to re-staging, or who are lost to follow-up before re-staging and are not known to have achieved at least a PR, or whose re-staging information is missing for any reason, will be considered to have not met the primary efficacy endpoint.

The primary efficacy analysis will be based on the calculation of the observed ORR and its posterior probability distribution. Evidence of efficacy of the ITD combination therapy will be based on two PoC criteria:

1. Observed ORR ≥ 60%
2. Posterior probability that the true ORR exceeds 45% is > 90% (given the observed data)

In addition, the percentiles of the posterior probability distribution for ORR, in particular the 95% uncertainty interval, defined by the 2.5 and 97.5 percentiles and also the posterior probability that the true ORR exceeds 45%, will be reported. The analysis will use a minimally informative prior distribution for the ORR, namely, Beta(a=0.86805, b=1) for which the median ORR is 45% and the amount of prior information is equivalent to approximately 1.87 (=a+b) patients.

If an interim analysis of ORR is required for any reason (e.g. a review of efficacy by the TMC or sponsor), the posterior probability distribution will be updated, using the minimally informative prior distribution and the accumulated data, and reported as appropriate.

Analysis of the secondary efficacy endpoints and quality of life endpoints will be conducted on the FAS. The clinical benefit rate (CBR) will be calculated as the number of patients who have experienced at least a minimal response (MR), divided by the number of patients registered on the trial. Patients who withdraw from the study prior to re-staging, or who are lost to follow-up before re-staging and are not known to have achieved at least an MR, or whose re-staging information is missing for any reason, will be considered to have not met this efficacy endpoint. The 95% uncertainty interval, defined by the 2.5 and 97.5 percentiles of the posterior probability distribution for CBR will be reported. The analysis will use a minimally informative prior distribution for the CBR, namely, Beta(a=0.86805, b=1) for which the median CBR is 45%.

Duration of response (DOR) will be measured from the date on which an overall response was achieved until the earlier of the date of progression or myeloma-related death. The study censor date for PFS (see below) will be used to censor DOR. Patients who have not progressed or died a myeloma-related death by the time of analysis (i.e. lost their response on or before the study censor date for PFS) will have their DOR censored at the study censor date for PFS.

PFS will be measured from the date of commencing ITD combination therapy until the earlier of the dates of progression or death from any cause. Patients who have not progressed or died at the time of analysis (i.e. on or before the study censor date for PFS) will have their PFS censored at the study

censor date for PFS. The study censor date for PFS is the earliest of the last dates of disease response assessment of those patients who remain on study (i.e. those patients who have not withdrawn or have not been deemed to be lost-to-follow-up). Patients who have withdrawn or have been lost to follow-up before the censor date will have their PFS censored at the date of their last disease response assessment on study. For each of these time-to-event endpoints (DOR and PFS), Kaplan-Meier (product-limit) estimates of duration times will be reported together with conventional 95% confidence intervals for the median duration time (using the Brookmeyer and Crowley method) and the survival function (using Greenwood's formula and the complementary log-log transformation). For patients with a BMAT at the time of the serological CR assessment, a landmark analysis of PFS will be conducted using a Cox proportional hazards regression model to investigate the association of PFS with the level of MRD.

The repeated assessment of quality of life will be analysed by fitting a linear mixed model. Details of these analyses of the secondary endpoints will be documented in the Statistical Analysis Plan (SAP) prior to locking the database for the primary efficacy analysis.

7.1.7 Safety Analysis

The co-primary objective of the trial is to evaluate the safety and tolerability of ITD combination therapy. These evaluations will be conducted on the Safety Set. Treatment emergent adverse events, i.e. newly occurring or worsening AE's that occur after the first dose of study drug, will be defined as per the CTCAE v4.03 and will be summarised by system organ class and/or preferred term as counts and percentages of participants with further subdivision based on severity and relationship to ITD therapy. Particular attention will be given to (i) rates of peripheral neuropathy (either sensory and/or painful) and cardiac toxicities ≥ Grade 2, (ii) cessation of ixazomib and/or thalidomide and/or dexamethasone due to unacceptable toxicity, and (iii) subject withdrawal due to unacceptable toxicity. Total dose and percentage of planned dose (PPD) will be summarized, by cycle, for each of ixazomib, thalidomide and dexamethasone and will also be summarized for the accumulated first 4 cycles of ITD therapy. PPD is the total dose delivered divided by the per-protocol planned total dose, expressed as a percentage. The summaries of total dose and PPD will consist of means, standard deviations, medians, 25th and 75th percentiles, minima and maxima. Listings of worst grades of toxicities, by patient and cycle and up to 30 days after the last dose of study drug, will be generated as an Appendix to the report

of the primary analysis and, as required, for the TMC or sponsor.

Adverse events will be tabulated according to the NCI CTCAE version 4(19), as a guideline, whenever possible will include the following categories:

Treatment-emergent AEs

- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by 10% of all patients)
- Serious adverse events

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

All patients who commence the combination therapy are in the "safety set" and will be included in these safety summaries until 30 days after they permanently cease one or more of the components of the combination. Thereafter, for patients remaining on just one or two of the agents, safety data will be reported in the form of listings. Newly emerging or worsening AE's that occur in the 30-day period after a patient permanently ceases one or more agents in the combination therapy will be included in both the tabular summaries for combination therapy and in the listings for single or double agent therapy.

If appropriate, additional safety summaries will be reported in order to more clearly enumerate rates of toxicities and to further define the safety profile of ixazomib.

7.1.8 Interim Analysis

Efficacy

Updating of the posterior distribution for ORR will commence after the first 12 patients have either

completed 4 cycles of therapy or withdrawn from the study, or earlier if requested by the TMC or sponsor. Publication of the posterior distribution for ORR will occur after all patients remaining on the study, at the time of the decision to close accrual, have completed 4 cycles of therapy or have subsequently withdrawn.

Safety Lead-in Evaluation

A safety lead-in evaluation will be performed by the Trial Management Committee (TMC) after the first 6 patients to commence ITD combination therapy have completed 1 cycle of ITD combination therapy or withdrawn earlier. The safety lead-in will be based on listings of adverse events and no formal statistical analysis is planned.

Continuous Monitoring and Early Stopping Rule

Safety will continue to be monitored after every additional cohort of 6 patients completes 1 cycle of ITD combination therapy or withdraws earlier, or, at anytime as requested by the TMC or sponsor. In particular, the rate of grade 3 or higher non-haematological toxicities will be monitored and the posterior probability that this rate exceeds 33.3% will be reported, based on a minimally informative prior distribution for the rate, namely, Beta(a=0.5, b=1) for which the median rate is 25%. The TMC or sponsor will consider early stopping or modification of the trial if the observed rate exceeds 35% and the posterior probability that the true rate exceeds 33.3% is more than 50%. For n=12 (or 36) patients, the probability that both these criteria are met is 0.05 when the true rate is 18.0% (or 22.9%) and 0.80 when the true rate is 49.9% (or 41.7%).

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

8.1.2 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.
- New primary malignancy (reportable for 3 years)

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as

serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.2 Procedures for Reporting Serious Adverse Events

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator Professor Andrew Spencer, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance (or designee):

> **Fatal and Life Threatening SAEs** within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4 as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

As all patients will be registered in, and must abide by the requirements of, the i-access® Risk Management Program, any possible exposure of a pregnant woman to thalidomide (even a single dose) must also be reported as per the i-access® Risk Management Program requirements.

SAE and Pregnancy Reporting Contact Information

Fax Number: 1-202-315-3560
Email: TakedaOncoCases@cognizant.com

Drug Safety Australia (Thalidomide)
Phone: 1800 235 436 (Option 4)
Fax: 1800 455 125
Email: drugsafety-australia@celgene.com

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

8.3 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue all study drugs. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the

Millennium Department of Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

- Pregnancy Report Form (provided by Millennium)

9. ADMINISTRATIVE REQUIREMENTS

9.1 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Millennium (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
• Phone: 1-844-N1-POINT (1-844-617-6468) • E-mail: GlobalOncologyMedinfo@takeda.com • FAX: 1-800-881-6092 • Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance

10. REFERENCES

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11. APPENDICES

11.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

11.2 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\,(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\,(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

11.4 IMWG Response Criteria

Adapted from International Myeloma Working Group uniform response criteria[1] and Kyle and Rajkumar[2].

1. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20(9):1467-73.
2. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23(1):3-9.

Stringent Complete Response (sCR)

CR as defined below plus

Normal FLC ratio and

Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence[1]

Complete Response[2] (CR)

Negative immunofixation on the serum and urine and

Disappearance of any soft tissue plasmacytomas and

<5% plasma cells in bone marrow[3]

Very Good Partial Response (VGPR)

Serum and urine M-protein detectable by immunofication but not on electrophoresis or 90% reduction in serum M-protein plus urine M-protein <100mg per 24 hour

Partial Response[4] (PR)

≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M protein by ≥ 90% or to <200mg per 24 hour

If the serum and urine M protein are unmeasurable[5], a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are

[1] Confirmation with repeat bone marrow biopsy not needed

[2] Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patient is defined as a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved FLC levels.

[3] Confirmation with repeat bone marrow biopsy not needed

[4] Confirmation with repeat bone marrow biopsy not needed

[5] In order to apply definition, patient must have measurable disease defined by at least one of the following:

- Serum M-protein ≥ 1g/dl
- Urine M-protein ≥200mg/24hour
- Serum FLC assay : Involved FLC level ≥ 10mg/dl provided serum FLC ratio is abnormal Bone marrow plasma cells ≥ 30%

unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%
In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.

Minor Response (MR)
≥25% but <49% reduction of serum M protein and reduction in 24 hr. M protein by 50-89%, which still exceeds 200mg per 24hr
In addition to the above criteria, if present as baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required.
No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

Stable disease (SD)
Not meeting criteria for MR, CR, VGPR, PR or progressive disease

Progressive Disease[6] (PD)
Any one or more of the following:
Increase of ≥25% from lowest response level in Serum M component and/or (the absolute increase must be ≥0.5g/dL)[7].
Urine M-component and/or (the absolute increase must be ≥ 200mg/24 hour.
Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >100mg/l.
Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[8].
Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
Development of hypercalcemia (corrected serum calcium > 2.65mmol/l) that can be attributed solely to the plasma cell proliferative disorder.

NOTE: The IMWG uniform response criteria have clarified that patients in CR need to meet the same criteria for disease progression as other patients not in CR for purposes of calculating progression-free survival and time to progression.
All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

[6] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy
[7] For progressive disease, serum M component increases of ≥1gm/dl are sufficient to define relapse if starting M-component is ≥5g/dl
[8] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse