CLINICAL STUDY PROTOCOL

Protocol number: X16032
Ixazomib for Treatment of Chronic Graft vs. Host Disease

Indication: Treatment of Chronic GVHD
Phase: Phase II

Protocol History

Original	30 April 2015
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This is an investigator-initiated study. The principal investigator, Stephanie J. Lee, MD, MPH (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: Ixazomib for Treatment of Chronic Graft vs. Host Disease

Phase: Phase II, single arm, open label, multi-center trial

Number of Patients: 50 total patients

Study Objectives

Primary Objective:

Determine the proportion of subjects with treatment failure by 6 months of Ixazomib treatment for chronic GVHD.

Secondary Objectives:

1. Determine 3 month overall (complete + partial), and complete response rate
2. Determine 6 month overall (complete + partial), and complete response rate
3. Report overall survival, non-relapse mortality, primary malignancy relapse, failure-free survival, treatment success, and discontinuation of immune-suppressive therapy at 6 months and 1 year
4. Examine functional outcome (2-minute walk test) and patient-reported outcomes (Lee Chronic GVHD Symptom Scale, quality of life (SF-36, FACT-BMT), Human Activity Profile (HAP)) at study enrollment, 6 months and 1 year
5. Study biologic effects of proteasome inhibition

Overview of Study Design:

This phase II trial will examine the efficacy of Ixazomib in chronic GVHD treatment. The primary endpoint is 6 month treatment failure.

Study Population:

Patients with chronic GVHD (diagnosed according to NIH Consensus Criteria) who have failed at least one prior line of systemic immune-suppressive therapy.

Duration of Study: Patients will complete up to 6 cycles of Ixazomib therapy and will complete 12 months of clinical follow up on study. At the 6 month time point, patients who have achieved a complete or partial response, or have stable disease, will have the option of receiving up to an additional 6 months of Ixazomib therapy.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BID	bis in die; twice a day
BM	bone marrow
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CR	complete response
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
ECG	Electrocardiogram
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
Hct	Hematocrit
IB	Investigator's Brochure
ICF	informed consent form
IRB	institutional review board
IV	intravenous; intravenously
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)

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Abbreviation	Term
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial response
PRO	patient-reported outcome
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
T_{max}	single-dose time to reach maximum (peak) concentration
ULN	upper limit of the normal range
US	United States
WBC	white blood cell

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1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Chronic graft vs. host disease

Chronic graft vs. host disease (chronic GVHD) is a major late complication of allogeneic hematopoietic cell transplantation (HCT) that affects up to 70% of HCT survivors. The syndrome is associated with major transplant-related morbidity, mortality, infectious complications, prolonged duration of immune suppression, and impaired patient-reported quality of life.[1-8] Thus, it represents a major obstacle to recovery and survival following HCT, and its prevention and treatment are of significant importance. The syndrome is characterized by diverse clinical manifestations, but the most commonly affected organs are the skin, eyes, mouth, and liver. However, most organs can be involved, with parallels to other systemic immune-mediated disorders.

Chronic GVHD diagnosis and classification

Diagnosis and classification of the syndrome has undergone major revision following the 2005 NIH Consensus Conference on Chronic GVHD. According to the historical classification, acute and chronic GVHD were distinguished by the occurrence of manifestations before or following day 100 post-HCT.[9] According to the proposed NIH Consensus definitions, the diagnosis of chronic GVHD is based on the presence of diagnostic manifestations of the syndrome, rather than the time of onset following HCT. Classic chronic GVHD is defined by the definitive manifestations of the syndrome in the absence of concurrent acute GVHD manifestations. Presence of both chronic and acute GVHD manifestations defines the overlap subtype of chronic GVHD. Chronic GVHD severity is scored according to objective criteria for each organ involved, which is summarized for an overall global severity score of mild, moderate, or severe.[10]

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Therapy of established chronic GVHD

Accepted standard primary therapy for chronic GVHD includes 1 mg/kg or greater of prednisone or equivalent with or without a calcineurin inhibitor.[2,11] The addition of other systemic immune-suppressive agents to initial therapy has not provided benefit, as evidenced by trials adding azathioprine, thalidomide, or hydroxychloroquine to initial treatment with steroids,[12-14] or the more recent randomized trial evaluating the combination of steroids and mycophenolate mofetil.[15] Published primary chronic GVHD therapy trials demonstrate that on average 27% will achieve complete response, and 60% will achieve overall response (complete + partial response) by 6-9 months after starting initial therapy.[11-16]

Based on insufficient response to primary therapy or a flare of chronic GVHD after tapering of initial therapy, many will go on to require additional immune-suppressive agents for chronic GVHD control. "Steroid-refractory" chronic GVHD has most commonly been defined as either progressive manifestations despite one month of treatment, or incomplete response despite two months of 1-2mg/kg of prednisone or equivalent.[2] In addition to steroid-refractoriness, other clinical indications for additional lines of systemic immune suppressive therapy include steroid dependence and steroid intolerance. Patients with steroid-dependent chronic GVHD can't tolerate tapering prednisone due to recurrent chronic GVHD manifestations. Steroid intolerant patients have medical complications of steroid therapy (e.g. hyperglycemia, edema, psychosis, osteoporosis), and thus require additional immune-suppressive agents to control GVHD and facilitate taper of prednisone. Multiple immune-suppressive therapies, including pharmacologic agents, monoclonal antibodies, and strategies such as extracorporeal photopheresis have demonstrated moderate activity in this setting, both ameliorating objective chronic GVHD manifestations, as well as facilitating taper of systemic steroids.[17] Their effectiveness is suboptimal, however, and many patients will require multiple agents to achieve disease control.

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The overall burden of chronic GVHD despite routine pharmacologic GVHD prophylaxis, limited response to primary and secondary therapy, and the attendant morbidity and mortality all support the need for novel approaches in chronic GVHD treatment.

Assessment of therapeutic response in chronic GVHD

The established method for response determination in the majority of chronic GVHD therapy trials is clinician-determined response. This method relies on the treating clinician's integration of dynamic chronic GVHD manifestations for a summary response categorization of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR indicates complete resolution of all chronic GVHD manifestations; PR signifies reduction in disease activity compared with pre-treatment levels, but without complete resolution; SD indicates no response and no progression; and PD indicates progressive chronic GVHD manifestations from baseline.

Following a 2005 NIH Consensus Conference for Chronic GVHD, several additional means of response assessment in chronic GVHD therapeutic trials have been proposed. These include change in overall NIH severity categories, proposed NIH response criteria, 0-4 and 0-10 ordinal scales that rely on clinician assessment, organ-specific tools such as the Vienna skin scale, as well as patient-determined change in chronic GVHD activity, chronic GVHD-associated symptom burden, functional limitations, and change in quality of life. The Chronic GVHD Consortium is currently assessing these competing measures of disease activity and their relationship to longer-reaching outcomes indicating clinical benefit, such as failure-free survival, discontinuation of all immune suppression, overall survival, or patient-reported benefit.

Interpretation of previously published trials for secondary chronic GVHD treatment is limited by a number of factors, most notably heterogeneity in response determination. A recently published large analysis has examined failure-free survival (FFS) as a proposed outcome among chronic GVHD patients treated with second-line systemic treatment. It

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included 312 patients who met the following criteria: (1) Had already received systemic steroid treatment for chronic GVHD at a prednisone-equivalent dose of at least 0.5 mg/kg/day, (2) also on an additional systemic immunosuppressive treatment when second-line treatment was started, and (3) received second-line treatment because of progressive GVHD manifestations after at least 1 week of initial treatment or because of lack of improvement after at least 2 weeks of initial treatment. Commonly used second-line treatments included mycophenolate mofetil, tacrolimus, sirolimus, extracorporeal photopheresis, cyclosporine, methotrexate, or other agents. By 6 months of second-line therapy, 44% had experienced treatment failure (composite of requirement of additional systemic immune suppression beyond second-line therapy, death, and malignancy relapse),[18] and thus 6 month failure-free survival (FFS) was 56%. In multivariate analysis, three factors were significant determinants of treatment failure: high-risk disease at transplantation (defined as diseases other than low risk; low-risk disease categories included chronic myeloid leukemia in chronic phase, acute leukemia in first complete remission, myelodysplastic syndrome without excess blasts, and non-malignant diseases), lower gastrointestinal involvement as second-line treatment was added, and severe NIH global score as second-line treatment was added. These three factors were used to define risk groups: low-risk had no risk factors, intermediate-risk included those with 1 risk factor, and high-risk included those with 2-3 risk factors. The cumulative incidence of 6 month treatment failure was 33% for low-risk, 41% for intermediate risk, and 56% for high risk.

Immune modulation following proteasome inhibition

Proteasome inhibition exerts powerful effects on immune cells implicated in GVHD pathogenesis. Pre-clinical and clinical data provide robust support for this concept.[19,20] Proteasome inhibitors interfere with antigen processing and presentation, as well as signaling cascades involved in immune cell function and survival: In dendritic cells (DC), there is impaired maturation, co-stimulatory molecule expression, and reduction of pro-inflammatory cytokines. T lymphocytes demonstrate apoptosis, reduced proliferation, impaired pro-inflammatory cytokine production, as well as expansion of regulatory T cells (Treg). B cell proliferation is decreased, and reduced antibody production is observed

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among plasma cells. Thus, proteasome inhibition targets key mediators established to be relevant in GVHD pathogenesis. In a murine GVHD model, bortezomib inhibited alloreactive T cells and protected from GVHD, did not adversely affect donor reconstitution, and did not impair cytotoxic T cell killing of tumor.[21]

Effect of proteasome inhibition on chronic GVHD in the clinical setting

While published clinical trials demonstrate the activity of proteasome inhibition in the primary prevention of GVHD,[22,23] less is known in the setting of chronic GVHD treatment. Emerging clinical data suggest that proteasome inhibition may control chronic GVHD: In a case report, a patient with relapsed multiple myeloma after HCT was successfully treated with bortezomib for oral lichen planus and biopsy-confirmed hepatic chronic GVHD.[24] In a case series (n=8), multiple myeloma patients were treated with bortezomib for relapsed disease after HCT, and those with chronic GVHD (n=4) experienced improvement.[25] Three had remission of chronic GVHD at a median of 150 days after bortezomib discontinuation, and one had recurrent ocular manifestations of chronic GVHD. Finally, in a larger series, 37 multiple myeloma patients with progressive or residual disease after HCT were treated with bortezomib. Of these, 8 patients had limited chronic GVHD, and 3 had extensive chronic GVHD. Patients were treated with a median of 6 cycles of bortezomib, and this was tolerated well. Common adverse events included peripheral neuropathy, mild thrombocytopenia not requiring transfusion, and fatigue, and there were no treatment related deaths. Of the 3 extensive chronic GVHD cases, 2 responded and were down-graded to limited disease at last evaluation. Of the 8 with limited chronic GVHD, none required additional immune suppressive therapy, and one had resolution of chronic GVHD.[26] Because these limited data are of interest but difficult to interpret in the setting of myeloma relapse or persistence, additional insight should arise from an existing chronic GVHD primary therapy trial (NCT00815919) testing the combination of prednisone and bortezomib.

1.1.2 Ixazomib

1.2 Preclinical Experience

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

1.3 Clinical Experience

As of 30 April 2012, 382 patients have been treated with Ixazomib across 9 enrolling, sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. Ixazomib is available as an intravenous and oral formulation. Regardless of the route of administration in the twice-weekly dosing schedule, Ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral Ixazomib has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions, the effect of food, and bioavailability also uses the oral formulation. Details of these trials can be found in ClinicalTrials.gov and the Ixazomib IB.

1.4 Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that Ixazomib (measured as the biologically active boronic acid form of Ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral Ixazomib is rapidly absorbed with a median time to first maximum plasma concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal $t_{1/2}$ after multiple dosing of approximately 5 to 7 days.[1] Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[2] Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for Ixazomib using the population PK analysis. Please refer to the current IB for information on the PK for IV doses of Ixazomib.

Metabolism appears to be the major route of elimination for Ixazomib, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes

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show that Ixazomib is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). Ixazomib is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for Ixazomib treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when Ixazomib is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of Ixazomib in human liver microsomes. Ixazomib may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. Ixazomib is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

1.5 Clinical Trial Experience Using the Oral Formulation of Ixazomib

In the 7 studies actively enrolling patients to investigate oral Ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of Ixazomib, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Ongoing Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 52	PO, weekly (W), single agent	0.24-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea
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*: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23 mg/m^2)
C16006 NDMM N = 28	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with melphalan and prednisone	Arm A*: 3-3.7 mg, fixed dose, TW DLT: rash, thrombocytopenia, subileus Arm B*: 5.5 mg, fixed dose, W DLT: Esophageal ulcer
C16007 RR-AL N = 6	PO, W, single agent	4-5.5 mg, fixed dose*, W MTD: 4 mg DLT: thrombocytopenia, dirrhea, dyspnea, acute rise in creatinine, cardiac arrest
C16008 NDMM N=11	PO, TW, combination with LenDex 21 day cycle	3.0-3.7 mg fixed dose* W MTD: 4 mg DLT:
C16009 Solid tumors, Lymphomas N = 22	PO, W, single agent	5.5 mg fixed dose* W
C16010 RRMM N = 1	PO, W, combination with LenDex	4.0 mg fixed dose* W
TB-MC010034 RRMM N = 5	PO, W, single agent in 1s part of study then in combination with LenDex in 2nd part	3.0 mg fixed dose* W DLT: thrombocytopenia, nausea, hypertension, diarrhea

Abbreviations: RRAL = Relapsed or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area ; DLT = dose-limiting toxicity; IV = intravenuously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RRMM = relapsed and/or refractory multiple myeloma; RPh2D = recommended phase 2 dose

* Approximate body surface area (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.

Overview of the Oral Formulation of Ixazomib

The emerging safety profile indicates that oral Ixazomib is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 2 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral Ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. 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 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (Oral Ixazomib Single-Agent [C16003/4/7/9] Safety Population)

Primary System Organ Class	Preferred Term and Incidence N=146 n (%)
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 102 (70)	Nausea 68 (47); Diarrhoea 55 (38); Vomiting 51 (35); Abdominal pain 21 (14); Constipation 21 (14)
General disorders and administration site conditions 98 (67)	Fatigue 71 (49); Pyrexia 31 (21); Oedema peripheral 15 (10)
Blood and lymphatic system disorders 77 (53)	Thrombocytopenia 60 (41); Anaemia 30 (21); Neutropenia 23 (16); Leukopenia 15 (10)
Nervous system disorders 63 (43)	Headache 20 (14); Dizziness 18 (12)
Metabolism and nutrition disorders 60 (41)	Decreased appetite 39 (27) Dehydration 21 (14)
Respiratory, thoracic and mediastinal disorders 60 (41)	Cough 22 (15); Dyspnoea 21 (14)
Skin and subcutaneous tissue disorders 60 (41)	Rash macular 17 (12)
Musculoskeletal and connective tissue disorders 56 (38)	Arthralgia 20 (14); Back pain 17 (12)
Infections and infestations 54 (37)	Upper respiratory tract infection 21 (14)

Source: Ixazomib Investigator's Brochure Edition 6

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

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

subjects as the denominator

In the 3 studies actively enrolling patients to investigate oral Ixazomib in combination with standard combination regimens in patients with newly diagnosed multiple myeloma, a total of 96 patients have been treated as of 30 April 2012. These patients have been treated with different doses of Ixazomib in combination with lenalidomide and dexamethasone in 2 trials (C16005 and C16008) and with melphalan and prednisone in 1 trial (C16006). The most frequent (at least 10%) adverse events occurring in the pooled safety population from Studies C16005, C16006, and C16008 is shown in Table 1-3. In combinations trials, related is defined as possibly related to any drug in the combination regimen, not just specifically related to Ixazomib.

Table 1-3 Summary of Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events (Oral Ixazomib Combination Agent [C16005/6/8] Safety Population)

Primary System Organ Class	Preferred Term and Incidence N= 96 n (%)
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhoea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)
Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anaemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);
Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

Source: Ixazomib Investigator's Brochure Edition 6.
Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.
Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

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 [3], non-Hodgkin's disease, Hodgkin's disease [4], relapsed and/or refractory multiple myeloma [RRMM; 5; 6], relapsed or refractory systemic light chain amyloidosis [RRAL; 7], and newly diagnosed multiple myeloma [NDMM; 8; 9; 10]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of Ixazomib.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent Ixazomib is administered weekly in patients with RRMM or RRAL, respectively.

1.6 Relapsed and/or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of Ixazomib administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral Ixazomib was determined to be 2.97 mg/m2.

Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of oral Ixazomib. The MTD expansion cohorts enrolling are:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];

2. Carfilzomib expansion cohort

3. Proteasome Inhibitor-Naïve expansion cohort

4. VELCADE-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest Ixazomib has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated.[11,12]

As of the 30 April 2012 data cut, these patients are considered heavily pretreated as evidenced by a median number of 4 (range 1–13) prior lines of therapy, with 66% refractory to the last line of therapy. Patients have received a median of 2 cycles of therapy (range, 1-11). Five patients have achieved objective response: 1 patient achieved a VGPR and 4 patients achieved a PR. Additionally, 15 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 15 patients remain on treatment; discontinuation of treatment was primarily due to progressive disease (69%).

A summary of the safety profile of patients treated in Study C16004 is outlined in Table 1-4. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

Table 1-4 Study C16004, Oral Ixazomib, Single Agent, Given Weekly: Most Common TEAEs as of 30 April 12 (N= 52)

Most Common (> 20%) Any Grade and Irrespective of Cause	Thrombocytopenia (54%) Fatigue (48%) Nausea (44%), diarrhea (44%) Vomiting (37%) Decreased appetite (33%) Rash* (31%) Anemia (25%) Neutropenia (23%)
Drug-Related Grade ≥ 3 in > 5% of patients	Thrombocytopenia (38%) Diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each) and vomiting 6%

Source: Ixazomib Investigator's Brochure Edition 6
* Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic,

pruritus,, rash erythematous, exfoliative rash, and rash popular

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to discontinue treatment included Grade 2 Ixazomib-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 Ixazomib-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and notrelated Grade 4 elevation in creatinine(1 patient each). There were no on-study deaths.

Study C16007 is evaluating single agent weekly , Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral Ixazomib was determined to be 4.0 mg. Following the establishment of the MTD, patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed.[13]

As of the 30 April 2012 data cut, the patients enrolled in the study are considered heavily pretreated, as evidenced by a median number of 3 prior lines of therapy (range 1–7), with 38% and 46% of patients having been previously treated with bortezomib and lenalidomide, respectively. To be eligible for the study, patients must have amyloid involvement of the

heart, kidney, or both; at the data cut the organ involvement distribution was 6, 4, and 4 patients, respectively. Patients have received a median of 2.5 cycles of therapy (range, 1-12). Eight patients remain on treatment. Early signs of activity have been reported. There were 11 patients who have received at least 1 cycle of therapy with completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at MTD is 56% (5 patients achieved a hematologic response [4 VGPR and 1 PR]; 3 patients showed no change, and 1 patient had an early progression.

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 1-5. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

Table 1-5 Study C16007, Oral Ixazomib, Single Agent Given Weekly Most Common TEAEs as of 30April 12 (N = 14)

Most Common (> 20%) Any Grade and Irrespective of Cause	Nausea (50%) Fatigue (36%) Thrombocytopenia (29%) Diarrhea (29%) Decreased Appetite (21%) Peripheral Edema (21%) Dyspnea (21%) Abdominal pain (21%)
Drug-Related Grade ≥ 3 in more than 3 Patients	Thrombocytopenia 5 patients, rash 3 patients, dehydration 2 patients, fatigue 2 patients

Source: Ixazomib Investigator's Brochure Edition 6

One patient discontinued study drug administration due to a TEAE (patient with DLT of acute rise in serum creatinine, dyspnea, and cardiac arrest treated at 5.5 mg, as noted above). No death has been reported.

The potential risks reported with Ixazomib use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the Ixazomib IB, SMA, and ICF documents. Regardless of whether Ixazomib is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible, and can be managed by routine

clinical monitoring and standard medical interventions, which may include dose reductions and supportive care. Please refer to the Ixazomib IB and SMA for further information.

1.7 Newly Diagnosed Multiple Myeloma (NDMM)

In Study C16005, Ixazomib is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to this study is closed.

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 mg/m^2 given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhoea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of Ixazomib at 2.97 mg/m^2 compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, Millennium designated 2.23 mg/m^2 as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 mg/m^2 has been translated into a fixed dose of 4.0 mg based on the results from the population PK analysis. Enrollment in this study has been completed; final study results are not available, but preliminary data suggests oral Ixazomib given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity.

In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral oedema (21%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with Ixazomib and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient.

A summary of the overall safety profile of patients treated in Study C16005 is outlined in Table 1-6. Overall, 100% of 65 patients experienced at least one TEAE of any grade and of any cause.

Table 1-6 Study C16005: Oral Ixazomib Given Weekly in Combination With Lenalidomide and Dexamethasone, Most Common TEAEs as of 30 April 2012

Most Common (> 20%) Any Grade and Irrespective of Cause	Fatigue (37%) Nausea (34%) Constipation (31%) Vomiting (28%) Diarrhoea (26%) Thrombocytopenia (23%) Upper respiratory tract infection (22%) Anaemia and oedema peripheral (20% each)
Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients	Nausea, vomiting (n=3 each) Thrombocytopenia, lymphopenia, rash pruritic (n=2 each)

Source: Ixazomib Investigator's Brochure Edition 6.

a Related means to ANY drug in the study drug combination.

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localised infection, gastrointestinal haemorrhage, respiratory syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhoea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.

As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal haemorrhage, angioedema, syncope, and RSV pneumonia.One death was reported for a patient with RSV pneumonia; the event was deemed by the investigator to be related to treatment with Ixazomib.

1.8 Study Rationale

The majority of patients with chronic GVHD will require additional treatment beyond first-line therapy, and novel therapies are needed in this setting to improve outcomes. Pre-clinical and clinical data demonstrate that proteasome inhibition produces an immunomodulatory effect relevant to GVHD control. Ixazomib is an oral proteasome inhibitor that has demonstrated an encouraging safety profile and efficacy in malignancy treatment in clinical trials. We propose a phase II trial of Ixazomib to examine its clinical and biologic activity in the treatment of advanced chronic GVHD.

1.9 Potential Risks and Benefits

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

Ixazomib is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, which has a known safety profile [VELCADE PI]. The most frequent AEs reported to date in the ongoing Ixazomib phase 1 studies were anticipated based on preclinical data and previous experience with VELCADE, and are noted in the IB and the informed consent documents. However, it is possible that Ixazomib will have toxicities that were not previously observed in or predicted from such sources. Patients will be monitored closely for toxicities.

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

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2. STUDY OBJECTIVES

2.1 Primary Objectives

Determine the proportion of subjects with treatment failure by 6 months of Ixazomib treatment for chronic GVHD.

2.2 Secondary Objectives

1. Determine 3 month overall (complete + partial), and complete response rate

2. Determine 6 month overall (complete + partial), and complete response rate

3. Report overall survival, non-relapse mortality, primary malignancy relapse, failure-free survival, treatment success, and discontinuation of immune-suppressive therapy at 6 months and 1 year

4. Examine functional outcome (2-minute walk test) and patient-reported outcomes (Lee Chronic GVHD Symptom Scale, quality of life (SF-36, FACT-BMT), Human Activity Profile (HAP)) at study enrollment, 6 months and 1 year

5. Study biologic effects of proteasome inhibition

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3. STUDY ENDPOINTS

3.1 Primary Endpoints

6 month treatment failure:

Defined by requirement for an additional line of systemic immune-suppressive therapy, recurrent malignancy, or death. Detailed definitions for systemic immune suppressive therapy and recurrent malignancy are provided below:

Systemic immune suppressive therapy:

It is expected that patients will be on additional systemic immune-suppressive agents at the time of enrollment, and management of those agents is not mandated by this protocol. Other agents can be tapered or discontinued as directed by the treating clinician.

Addition of new systemic immune-suppressive agents while on trial constitutes treatment failure, regardless of the indication for the agent. Systemic immune-suppressive agents include orally or intravenously administered systemically active immune-suppressive drugs, as well as procedures including extra-corporeal photopheresis (ECP).

Treatment failure does not include the following:

1. Adjustment of dosing of existing immune suppressive agents to maintain therapeutic drug levels (e.g. tacrolimus, cyclosporine, sirolimus), as this is standard practice.

2. Adjustment of prednisone dose up or down according to clinical judgment based on clinical manifestations of chronic GVHD and patient tolerance of steroid treatment. The management of prednisone will be directed by the treating clinician, and dose/duration of prednisone therapy is not mandated by this protocol.

3. Use of topical therapies, including:

    a. ocular drops or physical interventions (e.g. moisturizing eye drops, ocular cyclosporine drops, punctal plugs, scleral lenses, etc)

    b. oral rinses or agents (e.g. oral steroid rinse, oral topical immune suppressive agents)

    c. non-absorbable gastrointestinal steroid agents (e.g. beclomethasone, budesonide)

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d. topical agents applied to the skin (e.g. topical steroid creams, moisturizing lotion, topical immune suppressive agents such as tacrolimus)

e. topical agents applied to the vaginal mucosa (e.g. topical steroid creams or topical immune suppressive agents such as tacrolimus)

4. PUVA

5. Fluticasone, azithromycin, or monteleukast

Recurrent malignancy:

Defined as hematologic relapse or any unplanned intervention (including withdrawal of immune suppression) to prevent progression of disease in patients with evidence (molecular, cytogenetic, flow cytometric, radiographic) of malignant disease after transplantation.

1. The date of this event will be the earlier date of the following:
    a. Evidence of relapse
    b. Initiation date of intervention for treatment or prevention of relapse

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3.2 Secondary Endpoints

Failure-free survival

This time-to-event outcome will be estimated with the composite event of death from any cause, relapse or addition of secondary immune suppressive agents. This will be estimated at 6 months and 1 year.

Overall response rate

Overall response rate (ORR) at 3 and 6 months following initiation of Ixazomib represents the composite outcome of complete and partial response (CR + PR). ORR will be determined by clinician-defined categories of CR and PR, and separately calculated according to the proposed response definitions of the NIH Consensus Conference.

Complete response rate

Complete response (CR) at 3 and 6 months following initiation of therapy will be determined by clinician-defined CR, and separately calculated according to the proposed response definitions of the NIH Consensus Conference.

Cumulative incidence of non-relapse mortality and primary malignancy relapse

The cumulative incidence of non-relapse mortality (defined as death in the absence of primary malignancy relapse after transplant) and relapse (defined as hematologic relapse or any unplanned intervention to prevent progression of disease in patients with evidence (molecular, cytogenetic, flow cytometric, radiographic) of malignant disease after transplantation) will be estimated from time of Ixazomib initiation. These will be treated as competing-risk events, and estimated at 6 months and 1 year.

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Overall survival

Overall survival will be determined from date of Ixazomib initiation, with death from any cause as the event of interest, and censoring at last follow up date for those with incomplete observations. This will be determined at 6 months and 1 year.

Use of additional systemic immune suppressive therapies

The use of additional systemic immune suppressive agents will be captured at each study visit, as this constitutes treatment failure.

Discontinuation of all systemic immune suppressive therapies

The incidence of complete discontinuation of all systemic immune-suppressive therapies will be determined at 6 months and 1 year.

Treatment success

This endpoint will be estimated at 6 months and 1 year with a composite outcome of complete resolution of all reversible chronic GVHD manifestations, discontinuation of all systemic immune-suppressive agents, and freedom from death or primary malignancy relapse after transplant.

Patient-reported outcomes and functional measures

Patients will provide assessments of their functional ability (2-minute walk test), symptom burden, and quality of life using validated instruments recommended by the NIH Consensus Development Project on Chronic GVHD (Lee Chronic GVHD Symptom Scale, HAP functional scale, SF-36, and FACT-BMT). These will be studied at baseline, 6 months, and 1 year.

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Biologic studies

These studies aim to discern the biologic impact of proteasome inhibition in the treatment of chronic GVHD. Peripheral blood samples will be obtained at baseline (study enrollment pre-treatment), and then at the 3 and 6 month time points. An additional event-driven blood sample will be obtained when a new systemic immune suppressive therapy is added (treatment failure of Ixazomib). For each time point, whole blood will be collected in 2 PaxGene tubes for subsequent RNA extraction. Additionally, one 10cc heparin tube will be collected for processing of plasma. These starting materials will inform respectively (a) differential gene expression studies and (b) ELISA assays as predictive biomarkers of chronic GVHD therapeutic response.

4. STUDY DESIGN

4.1 Overview of Study Design

Single arm, phase II trial examining the efficacy of Ixazomib for treatment of chronic GVHD.

4.2 Number of Patients

A total of 50 patients will be enrolled. A patient is considered enrolled the day the informed consent form is signed. In order to control the speed of enrollment and ensure that no more than 50 subjects are enrolled across the study, each participant must be approved by the coordinating center at Fred Hutchinson prior to enrollment.

4.3 Duration of Study

Eligible patients will be enrolled, and undergo up to 6 cycles of study therapy. Clinical follow up will continue through one year after enrollment. Patients experiencing a CR, PR, or stable disease at 6 months will be given the option to continue on ixazomib for an additional 6 cycles (for a total of 12 cycles, or maximum 36 doses). These patients will return for a study assessment at 9 months, in addition to the 12 month visit for all patients. They will continue to complete Study Medication Diaries to track their doses, and will be required to continue to have a CBC checked before each cycle is dispensed. Patients who have a CR, PR or stable GVHD, and who have not started an additional systemic treatment for GVHD, can have a gap of up to two months between their 6^{th} and 7^{th} cycles of ixazomib. Patients who stop ixazomib after 6 cycles and then experience a *flare* of their chronic

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GVHD may re-start ixazomib as long as it has not been more than 1 month since their most recent dose of ixazomib, and as long as they have not started an additional systemic treatment for GVHD. No patient will remain on ixazomib past the 12 month time point; this means that some patients who elect to continue on ixazomib may not receive all six additional cycles.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Age 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 or exclusively non-heterosexual activity 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 two effective contraception measures during the entire study treatment period and through 90 days after the last dose of study drug, OR

- Agree to practice true abstinence or exclusively non-heterosexual activity 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 chronic GVHD according to the NIH Consensus Criteria.[10]

5. Patients must have failed at least one prior line of systemic immune suppressive therapy for management of chronic GVHD.

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 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 ≥ 30 mL/min (see Section 11.2).

5.2 Exclusion Criteria

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

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

2. Major surgery within 14 days before enrollment.

   - Does not include placement of venous access device, bone marrow biopsy, GVHD diagnostic biopsy, or other routine procedures in chronic GVHD or post-transplantation care.

3. Uncontrolled infection within 14 days before study enrollment.

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- Infection treated with appropriate antimicrobial therapy and without signs of progression/treatment failure does not constitute an exclusion criterion

4. 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.

    - Chronic hypertension on medical therapy does not constitute an exclusion criterion.

5. Systemic treatment, within 14 days before the first dose of Ixazomib, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

6. Active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

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

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

9. Non-hematologic malignancy within the past 2 years with the exception of:

    - adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer

    - carcinoma in situ of the cervix or breast

    - prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels

    - cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study

10. Patient has ≥ Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.

11. Treatment with non-FDA approved drug within 21 days of start of this trial

12. New systemic immune suppressive agent added for the treatment of chronic GVHD within 2 weeks prior to enrollment
    - Addition of a new systemic immune suppressive treatment simultaneously with ixazomib is also prohibited.

13. Evidence of recurrent or progressive underlying malignant disease.

14. Karnofsky performance status < 70%

15. Life expectancy less than 6 months

6. STUDY DRUG

6.1 Study Drug Administration

Ixazomib will be administered at 4mg oral dose once weekly on days 1, 8, and 15 of a 28-day cycle. Up to 6 total cycles of therapy will be delivered on trial, and patients will be followed through 1 year of total clinical follow up for study endpoints.

Patients experiencing a CR, PR, or stable disease at 6 months will be given the option to continue on ixazomib for up to an additional 6 cycles (for a total of up to 12 cycles, or maximum 36 doses). See section 4.3 for additional details.

Sufficient study drug will be dispensed at each study visit to cover one 28 day treatment cycle. Study patients will document their compliance through medication logs.

<u>Ixazomib Administration</u>

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 6.2). Due to the common side effect of nausea, it is recommended (but not required) that participants take Zofran (ondansetron) 8 mg PO, 30-60 minutes prior to each dose, and 8 hours after each dose. Additional doses of Zofran may be taken as needed, up to 24 mg in a 24-hour period.

The prescribed administration of Ixazomib doses in this study is 4mg oral dose once weekly on days 1, 8, and 15 of a 28-day cycle. Patients should be instructed to swallow Ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach. Patients should not have any food or drink (other than water) for at least 2 hours before taking drug, and for at least 1 hour after taking drug. A total of approximately 8 ounces (240 mL) of water should be taken with the capsule.

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, and removal and destruction will be documented on drug accountability logs.

6.2 Dose-Modification Guidelines

6.2.1 Recommended Ixazomib Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity

Treatment with Ixazomib will use a cycle length of 28 days. The next cycle should begin as soon as possible, but no later than 14 days after the end of the previous cycle. Unavoidable deviations from this schedule will be permissible with prior approval by the Principal Investigator or Study Chair. For a new cycle of treatment to begin, the patient must meet the following criteria within 3 days prior to drug being dispensed:

- ANC must be $\geq 1{,}000/mm^3$.

- Platelet count must be $\geq 75{,}000/mm^3$.
- All other non-hematologic toxicity (except for alopecia) must have resolved to $\leq$ Grade 1 or to the patient's baseline condition

These laboratory tests should be performed and reviewed at the study site.

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.

Ixazomib dose adjustments are described in table 6-1. For dosing recommendations for hematologic toxicities and non-hematologic toxicities, see Table 6-2 and Table 6-3 respectively.

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

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Table 6-2 Ixazomib Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count $\leq 30 \times 10^9$/L or ANC $\leq 0.50 \times 10^9$/L on a Ixazomib dosing day (other than Day 1)	• Ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated until the ANC and/or platelet counts have exceeded the prespecified values (see Section 6.2.1) • Upon recovery, Ixazomib may be reinitiated with 1 dose level reduction.
Dose Modifications for Subsequent Treatment Cycles	
• ANC $< 1.0 \times 10^9$/L, platelet count $< 75 \times 10^9$/L, or other non-hematologic toxicities > Grade 1 or not to the patient's baseline condition	• Hold Ixazomib until resolution as per criteria Section 6.2. • Upon recovery, reduce Ixazomib 1 dose level. • The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle: o If dose was reduced within the cycle, start the next cycle at that same dose. o If due to toxicity timing, ie, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce Ixazomib by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

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

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only [14]
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤ 1 or baseline • Resume at same dose level	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL) [14]
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated [14]
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	Symptomatic recommendations as per section 6.6	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Other Grade 3 non-hematologic toxicity judged to be related to study drug	• Hold study drug until resolution to Grade < 1 or baseline	Symptomatic recommendations noted in Section 6.6
If recovered to < Grade 1 or baseline within 4 weeks	Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline	

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

Adverse Event (Severity)	Action on Study Drug	Further Considerations
If not recovered to < Grade 1 or baseline within 4 weeks	• Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline	
Subsequent recurrence	• Follow above management guidelines	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	• Reduce study drug to next lower dose	
Grade 4 nonhematologic toxicities judged to be related to study drug	Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

Once Ixazomib is reduced for any toxicity, the dose may not be re-escalated.

6.2.2 Recommended Dose Modifications for <other drug(s)> Treatment Associated Toxicity

6.3 Excluded Concomitant Medications

The following medications are prohibited during the study:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. A Drug-Drug Interaction (DDI) with a strong inhibitor would increase MLN2238 exposure.

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided A DDI with a strong inducer would decrease MLN2238 exposure.

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
- The dietary supplements St John's wort and Ginkgo biloba .

6.4 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.
- 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.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.

6.5 Precautions and Restrictions

Fluid deficits should be corrected before and throughout treatment.

NSAIDs should be avoided in patients with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

Pregnancy

It is not known what effects Ixazomib has on human pregnancy or development of the embryo or fetus. Female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized

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 criteria:

- 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, 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 or exclusively non-heterosexual activity 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 postvasectomy), must agree to 1 of the following:

- Agree to practice two effective contraception measures during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence or exclusively non-heterosexual activity 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.)

6.6 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 Infection

Infection prophylaxis should follow institutional standards.

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Nausea and/or Vomiting

Standard anti-emetics may be used for prophylaxis and treatment of nausea or vomiting.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals. Fluid intake should be maintained to avoid dehydration.

Erythematous Rash With or Without Pruritus

Rash should be managed symptomatically according to standard medical practice, including supportive care, oral or topical steroids, and/or anti-histamines.

Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in Table 6-2 when thrombocytopenia occurs. Therapy can be reinitiated at a reduced level upon recovery of platelet counts.

Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Ixazomib administration should be modified when neutropenia occurs, as noted in the dose modification recommendations in Table 6-2. Therapy can be reinitiated at a reduced level upon recovery of absolute neutrophil counts. The use of growth factors (e.g. G-CSF) is permitted.

Fluid Deficits

Fluid deficits should be corrected before initiation of study drug and during treatment and as needed during therapy.

Hypotension

Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES) has been reported with Ixazomib. While this case ultimately resolved, PRES has also been reported rarely with another proteasome inhibitor, VELCADE. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

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.

6.7 Preparation, Reconstitution, and Dispensing

Ixazomib is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling Ixazomib capsules.

Millennium will ship study medication directly to participating sites, and notify Dr. Stephanie Lee when each shipment is made. See the Manual of Operations for more details.

6.8 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.

Ixazomib capsules should be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 2.3-, 3.0-, and 4.0 mg capsules are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet.

6.9 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.

6.10 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.

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6.11 Discontinuation of Ixazomib therapy

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. In the following circumstances, Ixazomib therapy will be discontinued, however active study follow up will continue until study-defined treatment failure occurs (i.e. death, relapse, or addition of a new systemic immune suppressive therapy). The End of Treatment visit should occur as soon as possible after ixazomib is stopped.:

- The treating clinician determines that the patient has responded to therapy and does not require any additional Ixazomib therapy
- Ixazomib therapy is discontinued due to unresolved toxicity
- Ixazomib therapy is discontinued due to patient non-adherence to therapy

6.12 Termination of study participation

The following conditions require discontinuation of Ixazomib therapy and/or termination of active study follow up:

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

- Ixazomib therapy is discontinued due to the addition of (or planned addition of) another line of systemic immune suppressive therapy
    - The End of Treatment visit should be completed as close as possible to the date that ixazomib is stopped. The date that the new systemic treatment is started should be recorded.
- The patient has relapse of their hematologic disorder or malignancy after transplant
    - The End of Treatment visit should be completed if possible.
- Death
- Completion of all study follow up

7. STATISTICAL AND QUANTITATIVE ANALYSES

7.1 Statistical Methods

7.1.1 Determination of Sample Size and planned methods of analysis

The primary endpoint is overall treatment failure at 6 months from study enrollment. Treatment failure represents the composite including addition of new line of systemic immune suppressive therapy beyond Ixazomib (objective signal of failure to control GVHD with Ixazomib), non-relapse death, and primary malignancy relapse.[29] The historical benchmark for this outcome based on this analysis of 312 chronic GVHD patients is a 6 month treatment failure rate of 44%. With 50 patients, the standard error of the estimated failure rate will be approximately 7 percentage points.

With 50 subjects and a 1-sided alpha of 0.1, there will be 82% power to detect a 15 percentage point reduction in the 6 month treatment failure rate, relative to the reference rate of 44%., based on an exact binomial calculation using that option in nQuery This reduction is deemed feasible based on the following: The major contribution to the observed treatment failure rate was 34% requiring additional immune suppressive therapy beyond second-line

therapy. Assuming effective therapy with ongoing Ixazomib over the treatment period could reduce this risk by 50% (i.e. to 17%) with little or no increased risk for relapse (3% in this published analysis) or non-relapse death (7% in this analysis), the overall improvement in the 6 month treatment failure rate could be 15%. Patients who are lost to follow up or otherwise not evaluable will not be replaced.

Although the overall 6 month failure rate in the historical benchmark study was 44%, this varied from 33% to 41% to 56% for patients that were classified as low, intermediate and high risk, respectively. Thus the relative proportions of patients in the different risk categories will need to be considered in order to interpret the possible benefit of Ixazomib therapy.

Time-to-event endpoints will be evaluated using Kaplan-Meier and cumulative incidence methods; response endpoints will be evaluated as proportions; patient-reported outcomes will be summarized as frequencies, or with mean and SD, as appropriate. The only comparative analysis will involve the biologic endpoints, where responders at 3 and 6 months will be compared to nonresponders, based on baseline values and on changes from baseline. This will involve standard parametric or non-parametric methods, depending on the observed distribution of these endpoints.

In the analysis of secondary objectives, we will study the 3 and 6 month overall (complete + partial) response and complete response rates, other efficacy measures listed above, patient reported outcomes, and biologic outcome measures. We will study association between biologic outcome measures and clinical parameters (response, treatment failure, mortality).

7.1.2 STUDY STOPPING RULES

While Ixazomib has demonstrated safety, it has not been previously studied in chronic GVHD therapy after allogeneic hematopoietic cell transplantation. Current evidence suggests that mortality after initiation of chronic GVHD therapy may be as high as 20% at 56 days in some high-risk patient groups (Blood and Marrow Transplant Clinical Trial Network Protocol 0801). In our current trial, we will implement a stopping rule based on a threshold rate of 10% treatment-related mortality occurring within 56 days (2 cycles) of starting treatment. If reasonable evidence exists that the rate on this trial exceeds this

threshold, then enrollment to the trial will be halted while data are reviewed. Reasonable evidence will be taken to mean that the lower bound of an exact 1-sided 80% confidence interval for the true non-relapse mortality rate exceeds 10%. The data will be evaluated at least every 10 patients, and will be triggered if 3 or more of 10, 4 or more of 20, 5 or more of 30, or 7 or more of 40 patients experience non-relapse mortality within the first 56 days.

Further details of the stopping rule include the following:

(a) Treatment-related mortality is any death occurring while receiving study drug, or within 30 days after discontinuation of study drug, that is possibly, probably or definitely related to the drug
(b) Relapse or progressive disease will factor into the attribution of cause, but will not automatically prevent a death from being classified as treatment-related
(c) For purposes of this stopping rule, the count of patients (10, 20, etc) will reflect the order in which patients start treatment
(d) If a DSMB review is required because the stopping rule is triggered, patients who are already enrolled and taking ixazomib may continue treatment, pending the outcome of that review. Any enrolled patient who has consented but not started study drug may not start ixazomib treatment, pending the outcome of that review.

In addition to this stopping rule, we will also implement a pre-approval process through the Coordinating Center at Fred Hutchinson to control the rate of enrollment on the trial and report to the DSMB all deaths that occur through 6 months of follow-up for all patients on trial (7 months for patients who complete the full 6 months of study treatment), so that these events can be reviewed and discussed by the DSMB if need be. For any DSMB review, we will provide an updated estimate of the cumulative incidence of treatment-related mortality for the entire trial.

The operating characteristics of this stopping rule are provided below:

True rate of event	Probability of stopping*	Average N at stopping*
0.05	35	49
0.10	25%	43

0.15	62%	34
0.20	87%	25
0.25	97%	19

*Based on 10,000 Monte Carlo simulations

8. ADVERSE EVENTS

8.1 Definitions

- **Pretreatment Event Definition**

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

- **Adverse Event**

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. It can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a drug whether or not it is related to the drug. 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.

<u>AE Grading Criteria:</u>

The study site will grade the severity of adverse events experienced by study participants on a scale from 1 to 5 according to NCI CTCAE v4.0 or current version. Grade 1 and grade 2

adverse events do not require reporting. Adverse events not included in the NCI CTCAE should be recorded and graded according to the General Grade Definition provided below:

ADVERSE EVENT GENERAL GRADE DEFINITIONS

Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE	Death related to AE

*Instrumental ADL: Preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL: Bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

○**Suspected Adverse Reactions – a subset of Adverse Events based on causality**

A suspected adverse reaction is any adverse event for which there is a *reasonable possibility* that the drug caused the event. *Reasonable possibility* means there is evidence to suggest a causal relationship between the drug and the event. Some examples are:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug. If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association, event recurs on re-challenge), a single case may be sufficiently persuasive. Often, more than one occurrence is needed before the sponsor-investigator can determine that there is a reasonable possibility that the drug caused the event.

- An aggregate analysis of events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a similar population not receiving the study drug.

If there is reason to conclude with certainty that the drug caused the event, the event is classified as an **Adverse Reaction**.

- **Unexpected**

An adverse event is considered unexpected *if it is not listed in the investigator brochure, or is not listed at the specificity or severity that has been observed in the event*. "Unexpected" also refers to adverse events that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

- **Serious**

An adverse event is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

1. Death
2. A life-threatening adverse event (places the subject at an immediate risk of death)
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant disability or incapacitation
5. A congenital anomaly or birth defect
6. 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.

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 Recording of Adverse Events

The study will collect all Grade 3 and above adverse events (*except* abnormal labs as outlined in section 8.1, and the exceptions listed below), regardless of relationship to study therapy or study procedures. Severity grading will be based on the current version of the Common Terminology Criteria for Adverse Events (CTCAE). Grade 1 and 2 events will not be collected.

Adverse events will be collected from the time the patient signs the informed consent until 30 days after the last dose of Ixazomib. Events that occur after this time will be recorded only if there is a reasonable possibility that the event was caused by a study procedure or Ixazomib. All recordable adverse events will be followed until resolution.

Reporting procedures:

- All non-serious, Grade 3 and above adverse events must be recorded in the database within 20 days of becoming aware of the event.

- Exceptions:

The following are frequent events in the chronic GVHD population and will not be recorded as adverse events *as long as they are not serious*:

- Abnormalities present at study enrollment: Will not be considered adverse events, unless such abnormalities worsen (i.e. increase in frequency, intensity, or present new complications or untoward events) during study follow up
- Electrolyte abnormalities: Increase or decrease in sodium, potassium, chloride, bicarbonate, phosphorus, magnesium, calcium, hyperglycemia following steroid

therapy

- Ocular: GVHD related eye dryness, discomfort, requirement for moisturizing eye drops or other topical GVHD ocular therapies or interventions (e.g. punctal plugs, scleral lenses), changes in visual acuity.
- Dermatology: Nail changes, GVHD rash (to include erythema, scleroderma, ulceration, lichenoid changes, hyper- or hypo-pigmentation, dry skin and alopecia) or cushingoid appearance due to steroid therapy.
- Gastrointestinal: Xerostomia, oral ulcers or other GVHD associated lesions, oral pain or sensitivity, anorexia, difficulty swallowing due to esophageal stricture or narrowing, nausea/vomiting, salivary gland changes, GVHD associated abdominal pain, bloating, diarrhea, weight loss
- Respiratory: shortness of breath, cough, or oxygen requirement associated with pulmonary chronic GVHD involvement
- Growth and Development: Reduced growth velocity, delayed puberty.
- Musculoskeletal changes: Avascular necrosis, fracture, arthritis, osteoporosis, decrease in range of motion associated with joint or fascial GVHD involvement
- Sexual Function: Erectile dysfunction, infertility, amenorrhea, vaginal stenosis, vaginal dryness or discomfort.
- Events secondary to routine procedures performed for chronic GVHD therapies: Extracorporeal photopheresis, PUVA therapy.

Non-serious adverse events collected in the database will be compiled by the coordinating center and reported to the DSMB approximately every 6 months.

All serious adverse events must be reported in the database within 24 hours of becoming aware of the event. Significant and relevant follow-up information should also be reported as soon as possible.

- Exception:
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

The database will notify the coordinating center and sponsor-investigator when a serious adverse event has been entered. The sponsor-investigator will then determine whether the event meets the criteria for expedited reporting (see below) and will work with the coordinating center to prepare the IND Safety Report.

8.3 IND Safety Reporting

An event must meet all three of the following criteria in order to qualify for expedited reporting to the FDA in an IND Safety Report:

1) Serious
2) Unexpected
3) Suspected adverse reaction (i.e. there is a reasonable possibility that the drug caused the event)

The sponsor-investigator is ultimately responsible for determining whether all criteria are met. Details are as follows:

- **Seriousness:** If either the sponsor-investigator or local investigator believes that an event is serious, it must be considered serious and evaluated by the sponsor-investigator for expedited reporting. Similarly, if either the sponsor-investigator or local investigator believes that an event is life threatening, it must be considered life threatening for reporting purposes.

- **Expectedness:** The sponsor-investigator is responsible for determining whether an event is unexpected.

- **Causality:** Although local investigators are required to provide a causality assessment for each serious adverse event originating from their sites, it is ultimately the sponsor-investigator who decides whether the event meets the definition of a suspected adverse reaction.

IND Safety reports will be submitted on a MedWatch3500A form to the FDA and all participating investigators no later than 15 days after the sponsor-investigator determines that the event qualifies for reporting.

- Exception: Fatal or life-threatening events will be reported within 7 days of when the sponsor-investigator receives notification of the event.

Relevant additional information should be submitted in a follow-up report as soon as possible, but no later than 15 days after the sponsor-investigator receives the information. All other adverse events that are collected by the study but do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

Notification of SAE that meet requirement for expedited reporting will also be provided to individual site principal investigators of this trial.

8.4 Reporting to Millennium

AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the date the participant signs Informed Consent 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 period must be reported, regardless of causality to study regimen. Additionally, if the investigator learns of a new primary malignancy occurring in a study participant within 3 years after the last dose of study drug, it must be reported to Millenium Pharmacovigilance.

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 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 (including serious pretreatment events) must also be reported to Millennium Pharmacovigilance:

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 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 specified in the protocol, 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 used at your institution, 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.

SAE and Pregnancy Reporting Contact Information

SAE and Pregnancy Reporting Contact Information
Fax Number: 1-800-963-6290 Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

- Oncology Electronic SAE Form with SAE Notification Form Cover Sheet (provided by Millennium)

8.5 Procedures for Reporting AEs

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 nonserious AEs , the investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

8.6 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, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (provided by Millennium). 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). 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 MedComm Solutions (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,
call MedComm Solutions at
877-674-3784 (877 MPI DRUG)
(US and International)

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 PPD.

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11. APPENDICES

11.1 Study Calendar

Procedure	Screening	Baseline	Study therapy (28 day cycles)											
			1	2	3	4	5	6	7	8	9	10	11	12
Ixazomib administration*			X	X	X	X	X	X	X	X	X	X	X	X
			Follow Up****											
			3 months			6 months			9 months▲			12 months		End of Treat-ment
Screening Procedures														
Eligibility criteria**	X													
Informed consent	X													
Efficacy Assessments														
Chronic GVHD activity - NIH score - clinician severity assessments - clinician response assessments		X	X			X			X			X		X
Patient- reported outcomes - QOL - HAP - Lee symptom scale -Patient-reported severity		X				X			X			X		X
Liver function tests		X	X			X			X			X		X
Functional measures - 2 minute walk test		X				X						X		
Record systemic immune suppressive agents		X	X			X			X			X		X
Blood samples (Two Paxgene tubes and one 10mL heparin tube)		X	X			X								X
Survival and malignancy relapse			X			X			X			X		X
Safety Assessments														
Pregnancy test	X													
CBC		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam		X	X			X			X			X		X
Adverse events***		X	X			X			X			X		

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*Ixazomib administration: Weekly for 3 weeks (day 1, 8, 15) out of each 28 day cycle for up to a total of 6 cycles of therapy (or 12 cycles if patient has CR/PR or stable disease at 6 months and chooses to continue on ixazomib). Acceptable window for each planned Ixazomib administration date is +/- 3 days, based on the day of the previous dose in the cycle. Unavoidable deviations from this dosing schedule must be approved by the Principal Investigator or Study Chair. Monitoring of routine laboratory tests (CBC, chemistry, LFT) are per institutional standards.

**Eligibility includes the following:

- Review of patient records for compliance with all listed inclusion and exclusion criteria
- Laboratory studies required to meet laboratory criteria
    - CBC, chemistry, liver function tests
- Confirmation of no history of HIV or hepatitis B/C
    - If HIV and hepatitis B/C testing has been previously done and documented in the patient record, new testing at time of eligibility screening for this study is not necessary
        - If HIV+, the patient is excluded
    - If Hepatitis B serology indicates prior infection (i.e. core Ab positive, or surface antigen positive), hepatitis B PCR testing on peripheral blood should be done.
        - If PCR negative, the patient is eligible, but if positive, ineligible.
    - If hepatitis C antibody testing is positive, hepatitis C PCR should be tested in peripheral blood.
        - If PCR negative, the patient is eligible, but if positive, ineligible.

***AE/SAE are monitored from the time the patient signs the consent document through 30 days following the final dose of study therapy

****Acceptable window for study visits at 3, 6, and 9 months is +/- 14 days, and acceptable window for the 12 month study visit is +/- 1 month. Study visit due dates are calculated based on the date of baseline visit, and 1 month = 28 days.

▲For patients who have a CR/PR or stable disease at 6 months, and who elect to continue on ixazomib for an additional 6 cycles, there will be an additional study visit at 9 months. This visit will occur at 9 months regardless of when the additional cycles of ixazomib are started.

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11.2 Cockcroft-Gault Equation

For males:

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

For females:

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

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

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