A Phase 2 Open-Label Pilot Study of the Safety and Tolerability of Ixazomib Administered Orally to Patients with Scleroderma-Related Interstitial Lung Disease

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1.0 INTRODUCTION

1.1 Background

Scleroderma is a chronic autoimmune connective tissue disease named for its progressive and often severe skin fibrosis. This illness is similarly known as systemic sclerosis because of its simultaneous involvement of internal organs by fibrosis particularly the lung, as well as the intestinal tract, heart, and kidneys. It is one of the more rare rheumatic diseases with a prevalence of approximately 1 of 4000 and an incidence of only 20 new cases per million/year in the US.

Initial skin involvement is manifest as an inflammatory non-pitting edematous phase. The skin subsequently becomes thickened and taut due to the deposition of collagen and extracellular matrix in the deeper dermis. Higher degrees of skin thickness result in significant morbidity due to compromised ability to maintain independent function. More severe skin thickness also associates with both greater frequency and severity of internal organ involvement and poorer prognosis [1]. Scleroderma patients, 80% of whom are females 30-50 years of age, have an overall 5 year survival rate of 75% from time of diagnosis [2]. Interstitial lung disease (ILD) /fibrosis is the foremost cause of scleroderma-related early mortality accounting for 35% of disease-related deaths [3]. Pulmonary artery hypertension and cardiac involvement are other frequent disease-related causes of death [3, 4]. The median survival for patients with scleroderma–related ILD is 5 to 8 years [5] and the extent of lung involvement has been directly correlated with the risk of death [6-9]).

1.2 Scleroderma Autoantibodies

As an autoimmune illness scleroderma is characterized by the production of autoantibodies which are useful clinically in diagnosing scleroderma and predicting the behavior of illness. Scleroderma antinuclear autoantibodies are detected in 80% of patients. Although ten scleroderma-specific antinuclear antibodies are currently known, 98% of patients will manifest only one of these different antibodies.

Associations have been observed between these autoantibodies and phenotypic behaviors of scleroderma in terms of skin severity as well as differing risks for scleroderma-related vascular and internal visceral complications. For example, RNA polymerase III antibody is commonly associated with very high skin thickness scores, high risk for renal crisis, and frequent gastrointestinal antral vascular ectasia (GAVE), but low risk for ILD. Scl-70 antibody is associated generally with moderate range skin thickness scores, high risk for ILD, and low risk for renal crisis. U3-RNP (fibrillarin) antibody is associated with lower range skin thickness and high risks severe ILD pulmonary artery hypertension, and scleroderma muscle involvement.

Scleroderma antinuclear antibodies pre-date illness and do not change type over the course of illness, including during treatment. Treatment does not significantly change the titer of antibody; consequently, serial monitoring of antibody titers is not used to gauge clinical responsiveness to immunosuppressive medications currently used for scleroderma care. Even though these antibodies have phenotypic associations with various skin and visceral organ features, they have been viewed as likely epiphenomena that are not implicated in

the pathogenesis of disease. But evidence to the contrary has been described for anti-fibrillarin 1 antibodies which induce fibroblast activation and overproduction of extracellular matrix with the release of TGF beta [10]. In addition, Scl-70 antibodies induced higher levels of type-1 IFN-α [11] as well as being demonstrated to directly amplify a fibrogenic cascade by interfering with the role of DNA topoisomerase I [12].

Further evidence for scleroderma being an antibody-mediated disease comes from studies of antibodies directed alternatively to various cell surface antigens and receptors, extracellular matrix components, and cytokine receptors instead of antinuclear antigens. Examples include anti-endothelial cell antibodies promoting endothelial cell dysfunction and apoptosis, and inducing adhesion molecules contributing to the vascular features of illness [13]. Endothelial antibodies also stimulate fibroblast proliferation and TGF beta and collagen production [14]. Autoantibodies directed against endothelial cell ICAM-1 cause pro-inflammatory activation of endothelial cells characterized by a significant increase in reactive oxygen species production and increased VCAM-1 expression [15]. Vascular injury is believed to be an early event in scleroderma resulting in endothelial cell activation and apoptosis, leading to inflammation and activation of T cells, B cells, and macrophages [16]. Other anti-endothelial cell antibodies are directed against angiotensin II type 1 receptor and endothelin 1 type A receptor with both antibodies biologically active in promoting inflammatory and fibrotic features [17]. Anti-fibroblast cell antibodies result in activation of skin and lung fibroblasts inducing both a pro-adhesive phenotype with up-regulation of ICAM 1 and increased production of proinflammatory cytokines IL-1 and IL-6 [18]. Anti-matrix metalloproteinase 1 (interstitial collagenase) and anti-matrix metalloproteinase 3 (stromelysin) antibodies inhibit normal turnover and degradation of extracellular matrix further promoting fibrosis [19, 20]. Anti-platelet derived growth factor receptor antibodies stimulate type 1 collagen gene expression and promote a myofibroblast phenotype in fibroblasts with increased α-smooth muscle actin expression [21]. Anti-estrogen receptor-alpha antibodies have been associated with diffuse cutaneous illness, Scl-70 antibody positivity, higher disease activity, increased T-cell apoptosis, and a higher number of activated Treg cells [22]. Other autoantibody targets include muscarinic-3 receptor, methionine sulfoxide reductase A and peroxiredoxin 1 enzymes involved in antioxidant repair, as well as the chemokine receptors CXCR3 and CXCR4 [23].

In general, these antibodies directed at various cell surface antigens and receptors, extracellular matrix components, and cytokine receptors are thought likely to have some pathogenic role. Also, different than antinuclear antibodies associated with scleroderma, these antibodies have not been sufficiently further studied and characterized to determine if they predate illness, change type over time, or change titer in response to immunosuppressive treatments.

1.3 Scleroderma Inflammation - Innate and Adaptive Immunity

Along with the multiple known autoantibodies thus far detected, additional alterations of both adaptive immunity and innate immunity have been described contributing to both the inflammatory and fibrotic features of scleroderma [24-28]. Some inflammation is still

present in fibrotic tissues as evidenced by the infiltration of plasmacytoid dendritic cells, macrophages, mast cells, CD4 T-cells, and activated B-cells [29].

1.4 Innate Immune System - Type 1 Interferon

The principal mediator of innate immunity is type-1 interferon (IFN). Interferon regulatory factors (IRFs) are transcriptional regulators of type-1 IFN and interferon inducible genes [30]. Genome wide association studies have linked genetic susceptibility of scleroderma to genes involved in the type-1 IFN signaling pathway, polymorphisms of *IRF5* (interferon regulatory factor 5), *IRF7*, and *IRF8*, and *STAT4* (signal transducer and activator of transcription 4) which is affiliated with adaptive immunity [31]. From microarray studies on scleroderma peripheral whole blood, a type-1 IFN signature is based on a pattern of increased expression of genes regulated by type-1 IFN and is present in blood even before overt skin fibrosis [32]. The presence of an IFN signature in scleroderma blood has been confirmed in monocytes and CD4+ cells [33, 34]

Tissue-infiltrating immune cells including pDCs, monocytes, macrophages, and stromal cells demonstrate innate immunity involvement by activated Toll-like receptor (TLR) signaling [35]. TLR4 signaling has been implicated in promoting unresolved and sustained tissue repair leading to persistent fibrosis [36]. TLR4 was overexpressed by macrophages, fibroblasts, and myofibroblasts in both scleroderma skin and lung tissues. Its expression in skin was seen to correlate with the severity of fibrosis clinically [37]. The overexpression of TLR4 has been also associated with increased downstream NF-κB signaling and activation of macrophages with a pro-fibrotic profile [38]. In addition, TLR9, TLR2, and TLR3 signal pathways have been associated with increased TGF-beta as a potent pro-fibrotic cytokine, NF-κB activation, and IL-6 and Type-1 IFN production [37, 39, 40].

Scleroderma vasculopathy primarily involves the small arteries and capillaries with obliteration of the vessel lumen hindering blood flow due to smooth muscle hypertrophy, intimal proliferation, and fibrosis. High serum levels of IFN-α were associated with scleroderma ischemic digital ulcers including digital loss [41]. Furthermore, in spite of the concentration of most circulating angiogenic factors being increased in scleroderma, low tissue capillary density is observed from nail fold capillary microscopy resulting from impaired formation of new blood vessels [42]. In addition to its role in the fibrotic manifestations of both skin and lung, type-1 IFN has been associated with impaired angiogenesis of new blood vessels and impaired arteriogenesis involving the remodeling of existing arteries [43]. Defective vasculogenesis in scleroderma is additionally thought due in part to a low absolute number of circulating endothelial progenitor (CEP) cells as compared with healthy controls [42]. IFN-α was demonstrated to decrease the number and function of bone marrow derived endothelial progenitor cells. Exceedingly low CEP numbers were associated with greater vascular manifestations including digital pitting and ulcers. In addition, the circulating endothelial progenitor cells present were observed to be impaired functionally, with diminished maturation potential to differentiate into endothelial cells.

1.5 Innate Immune System – Plasmacytoid Dendritic Cells

As part of the innate immune system, pDCs are considered to be the main source of type-1 IFN in scleroderma skin [11, 41, 44]. These cells are largely responsible for the IFN gene

expression signature observed in scleroderma which is present even before overt skin fibrosis [32]. PDCs can be activated by endogenous inducers including several autoantigens and autoantibodies [11, 41]. Serum containing Scl-70 (topoisomerase 1) antibody significantly induced higher levels of IFN-α as compared with other autoantibodies. The production of IFN-α was greater in patients with diffuse cutaneous as compared with more limited cutaneous illness, as well as being greater in patients with ILD.

PDCs in both scleroderma skin and blood also secrete chemokine CXCL4 /platelet factor 4 (PF-4) [45]. CXCL4/ PF4 levels are elevated in both the skin and serum in scleroderma, and further potentiate the ability of pDCs to secrete IFN-α [46]. In bleomycin-induced skin fibrosis model, depletion of pDCs attenuated skin fibrosis as well as the associated IFN-1 signature and CXCL4 expression [46].

PDCs additionally have been shown to induce plasmablast differentiation into Ig-secreting plasma cells through a sequential cooperation of the two secreted cytokines IFN-α and IL-6 [47].

1.6 IL-6

Interleukin-6 (IL-6) is one of the most prominent pro-inflammatory cytokines activated by the IFN pathway [48]. IL-6 is secreted by T helper cells, B-cells, fibrocytes, endothelial cells, and dendritic cells. Serum IL-6 levels were elevated in scleroderma patients [49]. Elevated serum levels of IL-6 were associated with higher scleroderma skin scores and worsened survival [50]. IL-6 levels were also associated with risk of progressive lung fibrosis with decreasing carbon monoxide diffusion capacity (DLCO) within the first year and subsequent greater mortality [51]. The production of both IL-6 and soluble IL-6R (sIL-6R) from peripheral blood mononuclear cells of scleroderma patients was increased [52]. Serum levels of sIL-6R correlated with the severity of scleroderma pulmonary fibrosis. Because sIL-6R acts as an agonist of IL-6 enhancing signal transduction, the findings suggested enhanced sIL-6R production may also be associated with the development of pulmonary fibrosis.

Scleroderma skin fibroblasts constitutively produce 30-fold more IL-6 than fibroblasts from normal skin [53]. In cultures, IL-6 increased fibroblast production of both collagen and glycosaminoglycan production [54]. Anti-IL-6 antibody used to block IL-6 response resulted in significant reduction of type 1 procollagen production and secretion by cultured scleroderma fibroblasts [55].

IL-6 was found to also promote the differentiation of CD4+ cells to the pro-fibrotic TH2 type while simultaneously suppressing TH1 differentiation [56]. IL-6 also induces the differentiation of B-cells into plasma cells and is shown to be critical to the survival of long-lived plasma cells [57, 58].

Use of the IL-6 inhibitor tocilizumab in both phase 2 faSScinate and phase 3 focuSSced clinical trials for patients with early scleroderma showed clinically meaningful although not statistically significant improvement of skin score after 24 and 48 weeks, respectively [59] [60]. Fewer patients treated with tocilizumab than the placebo experienced worsening in the percent predicted forced vital capacity (FVC) at 24 and 48 weeks respectively and fewer

patients receiving tocilizumab then placebo experienced an absolute decline of FVC by more than 10%, but again, not reaching statistical significance.

1.7 Macrophages

Macrophages are very heterogeneous and functionally distinguished in broad terms by the different activation expression profiles M1 and M2. A strong M2 signature has been observed in scleroderma blood, skin, and lung [61].

Serum levels of soluble CD163, a marker for M2 macrophages, are elevated in scleroderma. [62, 63]. Elevated soluble CD163 levels were found also elevated in urine as well as serum of scleroderma patients [64]. Elevated soluble CD163 levels in scleroderma were correlated with subsequent progression of disease [65].

CD163 expression was significantly greater in CD14+ peripheral blood mononuclear cells of scleroderma patients suggesting scleroderma monocytes had undergone differentiation into early macrophage activation [66]. *Siglec*-1 (CD169), a macrophage marker induced by type-1 IFN, also was increased in scleroderma CD14+ peripheral blood monocytes [34]. Cultured CD14+ monocytes from scleroderma patients with ILD as compared to those without revealed a pro-fibrotic phenotype characterized by greater CD163 expression and higher production of CCL18 and IL-10 in response to pro-inflammatory stimuli [67].

Macrophages infiltrate scleroderma skin [68, 69]. The number of CD163+ macrophages in scleroderma skin was increased not only in the perivascular regions but also particularly among thickened collagen bundles as compared with healthy controls [66]. Tissue-infiltrating macrophages located between collagen bundles in the dermis of scleroderma skin also expressed increased *Siglec*-1 (CD169), a macrophage marker induced by Type-IFN [34].

Macrophage M2 phenotype develops in response to several factors including TH2 cytokines IL-4, IL-10, and IL-13 promoting humoral immunity [70-72]. The serum levels of these cytokines are elevated in scleroderma [73-76]. M2 macrophages themselves are capable of secreting Il-4, IL-10, TGF-beta a pro-fibrotic cytokine, platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) involved with fibroblast activation during wound repair and tissue remodeling [77,78].

Additional genomic studies of scleroderma tissues provide evidence of innate immune system macrophage involvement. In scleroderma skin biopsies, macrophages demonstrated expression of both *Siglec-1* (CD169) and *IFI44* genes induced by type-1 IFN, which correlated with the extent of skin thickness [79]. Gene expression analysis of skin biopsies from multiple combined datasets showed very prominent IFN and IFN-inducible gene signatures in addition to a very prominent M2 macrophage signature as part of a fibroproliferative gene cluster specific to scleroderma [80]. An innate immune-fibrotic axis including both pro-fibrotic M2 macrophage and IFN was found to be shared in common among scleroderma skin, lung, and esophageal tissues as well as peripheral blood [81].

Nintedanib, a multi-tyrosine kinase inhibitor, was shown to inhibit M2 macrophage activation and polarization and to greatly reduce skin and pulmonary fibrotic manifestations

as well as pulmonary vascular disease in the Fra 2 mouse model of scleroderma [82]. However, the SENSCIS (Safety and Efficacy of Nintedanib in Systemic Sclerosis-Associated Lung Disease) clinical trial in scleroderma patients revealed somewhat heterogeneous outcomes in terms of clinical efficacy [83]. A clinically meaningful although not statistically significant slower rate of decline in FVC compared with placebo was observed. However, no other clinical benefits including skin were discerned. Even though the lung and skin have been reported to have the same innate immune-fibrotic gene signatures [81], the disparity in the clinical efficacy seen between the lung and skin in the SENSCIS study suggests there may be differences in the molecular pathobiology in various scleroderma tissues.

The faSSinate study using the IL-6 inhibitor tocilizumab provided useful insights regarding the role of IL-6 and macrophages in the pathogenesis of scleroderma [59]. From this study, tocilizumab was observed to down-regulate genes of skin M2 macrophages which was postulated to contribute to the skin softening observed. In addition, tocilizumab reduced the serum concentration of chemokine CCL-18 which was postulated to contribute to the trend observed toward helping preserve lung function. CCl-18 is secreted primarily by M2 lung alveolar macrophages and promotes collagen production by lung fibroblasts [84]. Higher serum levels of CCL18 in scleroderma were predictive of greater risk for progressing lung disease [85-87].

From the faSScinate study, the gene sets associated with fibrosis that were enriched in scleroderma skin biopsies at baseline also included those of M1 macrophages as well as M2 macrophages, TGF-beta, IL-6, and IFN-α [59]. M1 polarized macrophages reflect the classically activated, pro-inflammatory phenotype that develops in response to multiple factors including the TH1 cytokines, IFNγ, TNF-α, IL-1 beta, and IL-2 which also promote cell-mediated immunity [70,71,72]. At 24 weeks, tocilizumab resulted not only in downregulation of the expression of 16 genes found mostly within the M2-macrophage cluster, but also downregulation of the expression of two genes within the M1 macrophage cluster supporting a potential role for M1 macrophages in scleroderma. Tocilizumab did not downregulate gene sets on the skin related to TGF-beta and IFN-α.

The phenotypic and functional classification of M1 and M2 macrophages continues to undergo evolution. A spectrum of macrophage activation states in M2 macrophages and more so in monocytes/macrophages cells which co-express both M1 and M2 phenotypes was identified in the peripheral blood of scleroderma patients but not healthy controls [88]. Using flow cytometry surface marker analysis on peripheral blood from scleroderma patients with and without ILD, those patients with ILD had a significantly higher percentage of circulating monocyte/macrophage lineage cells expressing a mixed hybrid M1 and M2 phenotype [89]. This phenotype correlated with positive serum Scl-70 antibody, a scleroderma antinuclear antibody marker of greater risk for ILD [90]. M1-M2 hybrid phenotype likely reflects the plasticity of macrophages in various cytokine milieus [72]. The role and potential significance of macrophage plasticity in scleroderma remains unclear.

1.8 T-cells

Cutaneous infiltration in scleroderma was comprised predominantly by activated T-cells [91]. Skin CD 4+ helper T-cells in scleroderma are predominantly type 2 helper cells (TH2)

more so than type 1 helper cells (TH1) [92, 93]. TH2 helper cells promote humoral immune responses through the production of IL-4, IL-5, IL-6, IL-10, and IL-13 which are elevated in scleroderma [94, 95]. TH2 helper cells additionally secrete TGF-beta, a potent pro-fibrotic cytokine that is integrally involved in tissue repair and angiogenesis [96]. TGF-beta is increased in both scleroderma serum and fibrotic tissues [16].

1.9 B-cells

Studies have reported very few B-cells in scleroderma skin [29, 97]. In contrast, an activated B-cell signature was reported in scleroderma lesional skin [98]. Both diffuse B-cell infiltration and more focal B-cell lymphoid aggregates have been observed in biopsies of scleroderma-related lung disease [99].

Although peripheral memory B-cells were also found diminished in scleroderma [100], B-cells not only expressed increased levels of *B-cell activating factor* (*BAFF)* receptor, but also produced 38% more IL-6 and 35% more IgG when stimulated with *BAFF* as compared with healthy controls [101].

The expression of *BAFF* is increased in scleroderma skin [102]. *BAFF* expression is also elevated early in scleroderma serum correlating with type-1 IFN signature [32]. *BAFF* serum levels correlate with the extent of skin fibrosis, with increased *BAFF* expression in early scleroderma correlating with worsening mRSS and decreased *BAFF* expression correlating with improved mRSS over time [101]. Serum levels of *APRIL*, a proliferation-inducing ligand with close homology to *BAFF* that similarly serves as a B-cell survival factor, are also elevated in scleroderma [103]. However, *APRIL* levels did not correlate with *BAFF* levels and each showed distinct profiles with *APRIL* levels correlating with pulmonary fibrosis and high *BAFF* levels correlating with severe skin involvement.

Together, *BAFF* and *APRIL* have been determined to be critical to plasma cell survival by modulating the expression of antiapoptotic molecules [104].

Intravenous rituximab a monoclonal antibody depleting CD20+ B-cells has been investigated as potential therapy for scleroderma. Isolated case reports and a few small open-label uncontrolled studies have reported variable results [105-110]. Significant improvement in lung function was observed when rituximab was compared with placebo in a single center randomized controlled trial of 8 patients [111]. In a study using a nested case-control design, rituximab administered to 63 scleroderma patients significantly improved skin thickening in 25 patients and stabilized lung function at 6 months in 9 patients [112].

1.10 Plasma cells in Scleroderma

Although less extensively investigated than other immune cells, a role for plasma cells in scleroderma is supported by available reports. Mononuclear infiltrates in scleroderma skin were observed to be comprised of plasma cells as well as T-cells and macrophages [113-115]. Using whole-genome microarray analysis, a plasma cell gene expression signature was observed more highly expressed in both scleroderma skin and blood than in healthy donors [116].

From lung biopsies of non-specific interstitial pneumonia (NSIP) which is the most common form of ILD complicating scleroderma, plasma cells are the dominant inflammatory cells along with lymphocytes and macrophages infiltrating the alveolar walls and interstitium [117, 118].

Long-lived autoreactive plasma cells contribute to persistent autoimmunity by the continual secretion of autoantibodies [119]. In other illnesses they are observed to be resistant to the effects of conventional immunosuppressive agents including corticosteroids, cyclophosphamide, and rituximab [119]. These terminally differentiated and non-dividing memory plasma cells do not express CD20 on their cell surface and reside in survival niches within bone marrow and inflammatory tissues [58]. Additional cells including megakaryocytes and eosinophils appear essential to maintain a survival niche environment by producing plasma cell differentiating and survival factors *BAFF*, *APRIL*, and IL- 6 [58,104].

Autologous stem cell transplantation for scleroderma has emerged as a treatment option for those experiencing severe skin and/or lung illness [120]. The conditioning regimen used in the NIH protocol for autologous stem cell transplant in scleroderma (SCOT study) includes cyclophosphamide, equine ATG, and fractionated total-body irradiation. The outcomes of autologous stem cell transplantation as compared with oral cyclophosphamide for 1 year include better overall and event-free survival in addition to significant skin softening. In contrast, lung status pre-transplant is only stabilized in most instances. The irradiation used in the NIH conditioning regimen includes pulmonary and renal shielding, potentially leaving inflammatory niches which may contribute to 9% of transplanted patients requiring subsequent initiation of other immunosuppressive treatment due to relapsing illness. A scleroderma patient coming into my practice exhibited the persistence of high titer serum RNA polymerase III autoantibody after undergoing the NIH protocol for myeloablative autologous stem cell transplantation for severe scleroderma skin illness and with only modest improvement of skin thickening observed.

2.0 PROTEASOME INHIBITORS

Proteasomes are abundant in the cytoplasm and nuclei of cells; they maintain cellular viability and function by control of intracellular protein levels. When conjugated to ubiquitin, proteasomes catabolize intracellular proteins including proteins involved in cell division, proliferation, and apoptosis. Malignant plasma cells due to their rapid proliferation and protein secretion depend even more on proteasome function to remove mis-folded or damaged proteins [121].

Proteasome inhibition depletes both short-lived and long-lived memory plasm cells by interfering with the activation of anti-apoptotic NF-κB in concert with the accumulation of ubiquitinated proteins and/or misfolded proteins within the endoplasmic reticulum, in turn leading to activation of the terminal unfolded protein response and apoptosis of cells.

Two subsets of dendritic cells, pDCs which are the primary source of type-1 IFN in scleroderma and myeloid dendritic cells (mDCs), originate from a common hematopoietic progenitor cell [11, 41, 44, 122]. Among peripheral blood immune cells, pDCs were seen to be the most susceptible to bortezomib's apoptotic effect [123]. Bortezomib inhibited Toll-

like receptor signaling of stimulated pDCs as well as notably reduced the production of both IFN-α and IL-6, partially independent of pDC apoptosis that was induced.

Similar effects of proteasome inhibition have been observed on the survival and function of other immune effector cells besides plasma cells and pDCs including macrophages, T-cells, monocytes, B-cells, and osteoclasts [124]. Proteasome inhibition suppressed NF-κB activation in macrophages in association with reduced production of pro-inflammatory cytokines [125]. Proteasome inhibition of activated CD4+ T cells induced apoptosis while inhibiting the proliferation of those activated CD4+ T cells surviving proteasome inhibition [126]. The expression of surface receptor activation markers and the production of cytokines by surviving cells were also suppressed. The mechanisms of how the types of CD4+ T cells, such as TH1, TH2, follicular helper T cells, and Tregs respond variably to inhibition by the same proteasome inhibitor requires further study.

Proteasome inhibition has been studied in mouse models of systemic lupus erythematosus (SLE), another autoimmune inflammatory disease which like scleroderma portrays a type-1 IFN signature [127, 128]. PDCs in SLE are stimulated by endogenous nucleic acids and autoantibodies and produce IFN-α which is considered to play a key role in the pathogenesis of the disease. In a murine model of SLE, treatment with proteasome inhibitors prevented disease progression, and for already established disease markedly improved nephritis. Treatment resulted in significantly reduced plasma cell numbers with a greater reduction in autoreactive cells seen more so than the reduction in total IgG antibody secreting cells. This effect became more pronounced with longer treatment and was, in turn, reflected by lower serum autoantibody levels. As well, production of IFN-α by TLR-activated pDCs was suppressed due to a combination of reduced pDC survival and impaired pDC function [127].

Four patients with active SLE who had not responded to other treatments including cyclophosphamide and showed persisting autoantibody titers were treated with bortezomib resulting in significant clinical improvement and reduction in lupus autoantibodies [129]. Twelve patients with active, refractory SLE received a median of two cycles bortezomib with significant improvement in disease activity which remained stable for 6 months on maintenance treatments [130]. Seven of the patients became responsive to immunosuppressive treatment that had previously failed to control illness. A significant decline was observed in not only anti-dsDNA autoantibody but also anti-Sm/RNP and anti-SSA levels that typically do not vary in response to treatment. A lesser decline was seen in vaccine-induced protective antibody titers, remaining within the protective range for the majority of patients. Peripheral blood type-1 IFN level significantly declined.

3.0 SCLERODERMA INTERSTITIAL LUNG DISEASE TREATMENT

Therapeutic agents directed at either more general or more specific cellular, cytokine and chemokine targets have been studied in scleroderma. Corticosteroids, D-penicillamine, and interferon-γ lack proven efficacy. Methotrexate has clinically exhibited limited benefit on skin thickening and other visceral features of illness [131, 132]. The benefits of rituximab and tocilizumab remain uncertain [59, 60, 105-111]. More recently, a phase 2 study in early scleroderma using abatacept which blocks the co-stimulatory interaction of CD 80/86 on antigen presenting cells with CD28 on T-cells (ASSET trial) resulted in no statistically

significant difference in improvement of mRSS as compared with placebo at 12 months [133]. There also was no meaningful difference in the change of FVC % predicted. The RISE-SSc study of riociguat although showing a difference in skin thickness progression rate favoring riociguat versus placebo, the proportion of patients with ACR CRISS probability of improvement which includes FVC % predicted was the same at 1 year in both arms [134]. Based on the results of the SENSCIS trial (Safety and Efficacy in Nintedanib in Systemic Sclerosis-Associated Lung Disease) where the annual rate of decline in FVC was slower with nintedanib than with placebo, nintedanib was approved by FDA in 2019 to reduce the rate of SSc-ILD progression [83]. No clinical benefit from nintedanib was observed for other manifestations of scleroderma including skin. Nintedanib is the only drug FDA approved for progressive SSc-ILD. On the basis of this one study, it remains unknown which patients with SSc-ILD would benefit most from nintedanib and what would be the optimal timing of its initiation. Patients with SSc-ILD who demonstrate lung disease progression despite MMF or cyclophosphamide might benefit most from add-on therapy with nintedanib. Nintedanib may also be an alternative treatment consideration for SSc-ILD patients who are unable to take MMF or cyclophosphamide.

Two medications which have been utilized most extensively for treatment of ILD in scleroderma are cyclophosphamide more so in the past and mycophenolate currently. In the scleroderma lung study I (SLS I), oral cyclophosphamide resulted in statistically significant, although not clinically meaningful, slowing in the rate of decline of FVC % predicted relative to placebo, with a between group difference of only 2.53% in the corrected FVC % predicted at 1 year [135]. But at year 2 of follow-up, the difference between treatment arms was no longer sustained [136]. A 12 year followup study showed no differences in survival or rates of organ failure between the cyclophosphamide and placebo treatment arms [137]. Additionally, there are significant safety concerns for cyclophosphamide both in the short-term because of leukopenia, infections, and hemorrhagic cystitis, and in the long term based on complications including impaired fertility and hematologic, bladder and skin malignancies. Although only modestly clinically meaningful, the scleroderma lung study II (SLS II) found statistically significant benefit on the FVC % predicted from both mycophenolate taken for 2 years and oral cyclophosphamide taken for 1 year followed by 1 year placebo [152]. Mycophenolate was better tolerated with fewer treatment withdrawals, was safer with fewer drug-related adverse events, and was associated with fewer deaths. As a result, mycophenolate is the preferred initial treatment of choice for scleroderma-ILD even though it is still not FDA approved for treatment of scleroderma. More effective treatments for all facets of scleroderma including skin and lung are greatly needed.

4.0 RATIONALE FOR STUDY

Scleroderma is associated with a broad array of both antinuclear antibodies and antibodies directed against cell surface antigens and receptors, extracellular matrix components, and cytokine receptors. The antinuclear antibodies which are useful clinically because of their associations with various phenotypic behaviors of scleroderma share similar behaviors of predating clinical illness and remaining of the same specificity unchanged in any individual patient over many years' time, including during periods of treatment. These serum

antibodies also share the similar behavior of not being significantly reduced in titer in response to existing immunosuppressive treatments used for the management of scleroderma including cyclophosphamide. Persisting scleroderma autoantibody has been observed following myeloablative autologous stem cell transplant which utilizes lung and kidney shielding.

Collectively, these observations are consistent with long-lived plasma cells being a potential source of scleroderma antinuclear antibodies. Long-lived autoreactive plasma cells contribute to autoimmunity by the continual secretion of autoantibodies [119]. These terminally differentiated and non-dividing memory plasma cells have been shown to reside in survival niches within bone marrow and inflammatory tissues in other illnesses [58]. As such, they have been observed to be resistant to the effects of conventional immunosuppressive agents including corticosteroids, cyclophosphamide, and rituximab.

Plasma cell infiltration is present in scleroderma skin as well as in lung tissue where plasma cells are one of the most predominant cells observed pathologically [113-115] [117, 118]. Persisting inflammatory niches in lung, kidney, and potentially bone marrow may potentially contribute to the 9% relapse rate observed following myeloablative autologous stem cell transplantation for scleroderma where the conditioning regimen of cyclophosphamide, equine ATG, and fractionated total-body irradiation includes shielding of lungs and kidneys. In addition to lung fibrosis, persisting inflammatory niches in the lung tissue may potentially contribute to the observation of the pulmonary status being only stabilized in most instances following autologous stem cell transplantation, in contrast to the more significant improvement commonly observed in skin thickening.

A type-1 IFN signature based on a pattern of increased expression of genes regulated by type-1 IFN has been found prominent in scleroderma skin, lung tissue, and blood. The primary source of IFN in scleroderma is pDCs [11, 41, 44] which are found activated in scleroderma skin, lung, and blood. Type-1 IFN expressed by pDCs promotes humoral responses by either directly acting on B cells [47] or by enhancing follicular help T cell (TFH) responses which are essential for germinal center reaction as well as for the generation of high affinity antibody responses [138-140]. Furthermore, type-1 IFN can also induce OX40L expression on mDCs [140] which play an important role in the enhancement of TH2-type T cell responses and increased antibody responses. OX40L expression has also been reported to be associated with the pathogenesis of inflammation-driven fibrosis [141], although a recent study suggested that serum OX40L levels might not be an ideal serum biomarker for scleroderma-associated ILD in patients [142]. However, this study reported that CCL18 can be a potential predictive biomarker for progression of ILD in scleroderma. In addition, serum epithelial-derived surfactant protein D (SP-D) is a relevant diagnostic biomarker for scleroderma-associated ILD, whereas Krebs von den Lungen 6 glycoprotein (KL-6) could be used to assess the severity of lung fibrosis. Nonetheless, it might be still important to test OX40L expression level on mDC cell surface.

Proteasome inhibitors have been shown highly effective in depleting both short-lived and long-lived memory plasma cells. Proteasome inhibitors also have effects upon the function and survival of additional immune cells including pDCs and others [124-127]. Proteasome

inhibitors targeting plasma cells and other immune cells have not been studied in scleroderma. Proteasome inhibition could potentially influence the immunopathogenesis of scleroderma through combined effects on both adaptive and innate immune mechanisms of the illness.

Precedence for the use of proteasome inhibitors comes from studies of bortezomib in SLE, where proteasome inhibition resulted in reduced production of autoantibodies and reduced levels of IFN-α as a pro-inflammatory mediator thought to play a similarly important role in its pathogenesis [129, 130].

Ixazomib is the first oral proteasome inhibitor approved by the FDA in November 2015 for the treatment of multiple myeloma (MM) in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy. In addition to inhibiting plasma cell proliferation by induction of apoptosis, ixazomib in multiple myeloma also interfered with the cytoprotective effects of the bone marrow microenvironment sustaining a framework promoting plasma cell proliferation, stromal cell interactions, and tissue hypoxia which augment drug resistance.

5.0 POTENTIAL BENEFITS AND RISKS TO HUMAN PATIENTS

The dosing schedule of ixazomib selected for this study is the same as the FDA approved dosing schedule of ixazomib for the treatment of multiple myeloma [143]. Ixazomib 4 mg will be taken orally by all study participants on days 1, 8, and 15 of a 28-day treatment cycle repeated for 6 cycles. This study will not be using ixazomib in combination with lenalidomide or dexamethasone. The primary objective of this study is to determine the safety and tolerability of ixazomib when administered to 12 adult patients with scleroderma-ILD. Ixazomib will be administered alone in 6 patients not on scleroderma-ILD background medication at study entry and in 6 patients already using a stable background dose of MMF for at least 3 months prior to study entry. MMF background use is permitted for 6 participants because of it being the most common treatment used for SSc-ILD and the importance of determining the safety and tolerance of ixazomib in this clinical context.

Pharmacokinetic studies show ixazomib to be absorbed rapidly. Maximal concentration was observed at 1 hour. Its half-life ranges 3.3-7.4 days following a dose of 0.48 mg/m^2. From Phase II and phase III clinical trials, side effects were considered manageable and infrequent including thrombocytopenia, leukopenia, rash, nausea, diarrhea, fatigue, and peripheral neuropathy [144]. Clinical trials in multiple myeloma showed ixazomib had a lower incidence of peripheral neuropathy compared with bortezomib [145].

In evaluating the safety and tolerability of ixazomib in patients with scleroderma, the multi-organ involvement associated with the illness must be taken into consideration. Scleroderma is often associated with gastrointestinal dysfunction including esophageal dysmotility and gastroesophageal reflux disease; this may put patients at greater risk for some of the gastrointestinal adverse events associated with ixazomib e.g., nausea, dyspepsia, or vomiting.

This study will enroll 6 participants who are already being treated with MMF at a stable maximum dose of 1500 mg BID for the 3 months preceding study entry. Ixazomib has not

been studied when given concurrently with MMF. Therefore, the primary objective of this study is to assess the safety and tolerability of ixazomib alone and when administered concurrently with MMF. MMF has a safety profile that overlaps with the safety profile of ixazomib, particularly in regards to hematologic, gastrointestinal, and liver effects, and peripheral edema. In addition, the safety profiles may overlap in other ways which are not foreseen. The present safety and tolerability study incorporating careful safety monitoring will aid in assessing the potential significance of any overlap in the safety profiles of ixazomib and MMF.

As well, there are potentially important differences between multiple myeloma and scleroderma-ILD patient populations regarding both demographics and comorbidities. Ixazomib is approved for treatment of multiple myeloma in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy. Multiple myeloma is somewhat more common in men than women (1.4:1). It is an illness of older adults having a median age at diagnosis of 66 years; only 10% of patients are younger than age 50 years, and only 2 % are younger than 40 years [146]. Compared with myeloma patients, the scleroderma-ILD population is younger with the diagnosis of scleroderma most often occurring between the ages of 30 and 50 years, and more predominantly in women. A case series of 60 scleroderma patients demonstrated that 28 % had clinical and/or electrophysiological evidence of peripheral neuropathy [147]. Those with peripheral neuropathy were more likely to be male, African American, to have diabetes mellitus, to manifest anti-U1 RNP scleroderma autoantibody, and to have the limited cutaneous form of systemic scleroderma which is not eligible for this study. As well, a potential non-scleroderma etiology for the peripheral neuropathy such as diabetes mellitus was identified in 82.3% of those scleroderma patients.

Should ixazomib administered alone or concurrently with MMF be demonstrated to have an acceptable safety and tolerance profile in patients with SSc-ILD, this study may offer insights important to the design of subsequent clinical trials evaluating ixazomib as a therapeutic alternative or addition to existing therapies for this serious illness

6.0 STUDY OBJECTIVES

6.1 Primary objective:

To determine the safety and tolerability of ixazomib 4 mg taken orally on days 1, 8, and 15 of a 28-day treatment cycle repeated for 6 cycles when administered to adult patients with scleroderma−related ILD as assessed by:

1. Physical examinations, vital signs, 12-lead ECG, echocardiogram, clinical laboratory tests, and pregnancy tests.
2. UCLA SCTC GIT 2.0 questionnaire [148, 149].
3. Averse event documentation.

6.2 Secondary Objective

To determine the clinical efficacy of ixazomib 4 mg taken orally on days 1, 8, and 15 of a 28-day treatment cycle repeated for 6 cycles when administered to adult patients with scleroderma-related ILD as assessed by:

1. ACR CRISS (American College of Rheumatology Composite Response Index for clinical trials early diffuse cutaneous Systemic Sclerosis) [150].
2. Each of the individual components of ACR CRISS: mRSS (modified Rodnan skin score), FVC % predicted, HAQ-DI (Health Assessment Questionnaire-Disability Index), PtGA (Patient Global Assessment), MDGA (Physician Global Assessment).
3. DLCO % predicted.
4. High resolution CT (HRCT) chest scan ILD severity using the Goh scoring method [6].
5. Additional patient reported outcome Mahler Baseline/Transitional Dyspnea Index (Mahler BDI/TDI).

6.3 Exploratory Objectives

To determine the immunologic effects of ixazomib 4 mg taken orally on days 1, 8, and 15 of a 28-day treatment cycle repeated for 6 cycles when administered to adult patients with scleroderma-related ILD as assessed by:

1. Skin biopsies for histology, immunohistochemistry, gene expression (RNA-seq), and proteomics analysis related to plasma cells, pDCs, mDCs, and macrophages; cytokines including IFN and IFN gene signature; and scleroderma biomarkers.
2. Whole blood samples for flow cytometric analysis of immune cells including subsets of dendritic cells, monocytes, T-cells, B-cells, eosinophils, mast cells, and other immune cells, including innate lymphoid cells (especially ILC2); and whole blood transcriptome analysis.
3. Serum for cytokine and chemokine analysis including IL-6, IFN, and related cytokine levels; scleroderma-related autoantibody diversity and titers, and scleroderma biomarkers.

7.0 STUDY DESIGN

7.1 Overview

This is a phase 2 open-label, safety and tolerability pilot study of oral ixazomib in patients with scleroderma-ILD (SSc-ILD). Planned enrollment will be 12 patients who have been seen in the Mayo Clinic Arizona Scleroderma program among whom will be 6 participants already taking SSc-ILD background medication mycophenolate (MMF) at stable dose for at least 3 months, and 6 participants who either have not taken a SSc-ILD background medication within 3 months of study screening or by the time of study screening will complete medication washout of medications being taken for SSc-ILD other than MMF. The number of study candidates needing to washout medications other than MMF is anticipated to be very low based on the low prevalence of medicines other than MMF used clinically for the treatment of scleroderma-ILD. No study candidate already taking MMF will be asked to wash out MMF. Eligible participants include male and female adult patients at least 18 years of age, fulfilling the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for systemic sclerosis/scleroderma [151] and having disease duration ≤ 60 months based on first non-Raynaud's phenomenon manifestation. ILD is based on features observed from the participant's HRCT chest scan obtained within 3 months prior to either medication washout or screening visit, as applicable. Studyscreening

will include pulmonary function testing demonstrating FVC ≥45% predicted and DLCO ≥40% predicted, which will also be determined to be stable measurements as compared with previous pulmonary function testing obtained clinically within the prior 3-12 months. For the 6 study participants who are taking stable dose background MMF, the MMF will be continued at the same dose during the study. MMF will be prescribed as routine clinical care and will not be provided as part of the study. All 12 participants will be administered oral ixazomib. Ixazomib dose modification or interruption will be allowed for safety or tolerability reasons at any time during the study. Any patient who permanently and prematurely discontinues study treatment will also be discontinued from the study.

There are four study periods (all durations are in calendar days):

- **Washout Period:** ≤ 90 days:
    - **Participants who are taking background SSc-ILD medication other than MMF at screening:**

      Washout will be required for: a) patients taking medication specifically for SSc-ILD other than MMF (See 8.2.4 Eligibility Criteria Medication Exclusions); b) patients taking any other excluded medication (See 8.2.4 Eligibility Criteria Medication Exclusions); and c) patients who smoked tobacco in the 90 days before screening.

    - **Participants who are taking background MMF at screening:**

      Washout will be required for: a) patients taking an excluded medication (See 8.2.4 Eligibility Criteria Medication Exclusions); and b) patients who smoked tobacco in the 90 days before screening.

- **Screening Period:** ≤21 days
- **Treatment Period:** includes initiation and subsequent use ixazomib for six cycles (each cycle is 28 days duration)
- **Post-treatment Follow-up Period:** 28−35 days after completion of last cycle

Scheduled study visits will be at the start of the washout period, at screening, at study day 1, day 28 (week 4), day 56 (week 8), day 84 (week 12), day 112 (week 16), day 140 (week 20), and day 168 (week 24 end of treatment), and day 196-203 (post-treatment follow-up visit 28 to 35 days after completion of the last cycle).

Additional lab test visits are scheduled day 14 (week 2), day 42 (week 6), and day 70 (week 10) for hematology and chemistry tests monitoring during the first three ixazomib cycles.

Patients requiring medication washout will return at the end of the washout period for the screening visit; all other eligible patients will begin study participation with the screening visit.

7.2 Rationale for Study Design

This is an open-label safety and tolerability pilot study of oral ixazomib in patients with SSc-ILD. An ixazomib dose of 4 mg orally on days 1, 8, and 15 of a 28-day treatment cycle for 6

cycles will be evaluated. This dose is approved for the treatment of multiple myeloma in combination with lenalidomide and dexamethasone in patients who have received at least 1 prior therapy [143].

A six cycle treatment duration was chosen in light of the improved safety profile of oral ixazomib over the earlier proteasome inhibitors bortezomib given either intravenously or subcutaneously and carfilzomib given intravenously particularly in regard to the potential adverse effect of peripheral neuropathy. The common and expected adverse effects have been shown to manifest most often in the initial months of treatment.

To accommodate current approaches to the treatment of SSc-ILD, the study will include 6 study participants taking a stable oral dose of MMF for at least 3 months with ixazomib added to their ongoing treatment, and 6 study participants not receiving treatment specifically for SSc-ILD at study screening. The maximum dose MMF (≤1.5 g BID) in this study is based on the dose most frequently used in patients with SSc-ILD. This is the same dose used in the randomized, double-blind, controlled Scleroderma Lung Study-II (SLS II) study comparing oral cyclophosphamide for 1 year plus 1 year placebo with MMF for two years [152].

8.0 STUDY POPULATION

8.1 Inclusion Criteria

Patients who meet *all* of the following criteria are eligible to participate in the study:

8.1.1 Demographic Characteristics:

1. Male and female patients, age ≥18 years at time of signing informed written consent

8.1.2 SSc and SSc-ILD Related Criteria:

2. Confirmed diagnosis of diffuse cutaneous systemic sclerosis/scleroderma fulfilling the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for systemic sclerosis/scleroderma [151].

3. Disease duration ≤60 months defined as the time from the first non-Raynaud's phenomenon manifestation.

4. mRSS ≥15 and ≤ 45

5. Diagnosis of SSc-ILD based on a HRCT chest scan completed within 3 months prior to the date of written informed consent at medication washout or screening, as applicable. The HRCT chest scan must demonstrate features consistent with SSc-ILD, as confirmed following review of the HRCT images by Mayo radiology study staff. If the HRCT chest study is determined to be technically inadequate (for example, prone imaging not included), or cannot be made available for review by Mayo radiology study staff, or if the HRCT chest was performed more than 3 months prior to signing of written informed consent, a HRCT chest scan will be obtained during study screening.

6. Screening pulmonary function testing demonstrating FVC ≥45% predicted and DLCO ≥40% predicted. Pulmonary function testing previously completed as part of clinical care within the prior 3-12 months will be used to compare screening results with prior testing to determine there has not been an interim decline of FVC ≥15 % predicted or decline of DLCO ≥ 15% predicted. Only if both FVC % predicted and DLCO % predicted are observed clinically stable will the patient be considered eligible for participation.

7. Screening resting transthoracic echocardiogram within 6 months of providing written informed consent at medication washout or screening, as applicable, demonstrating estimated right ventricular systolic pressure of ≤ 40 mm Hg, no evidence of right atrial or right ventricular enlargement, and left ventricular ejection fraction ≥ 40%.

8. At study entry, the participant is either not taking any background SSc-ILD medication or is taking background MMF, as described below:

a. Not on background SSc-ILD medication

Participant has not taken background medication specifically for SSc-ILD in the 3 months before study screening or will complete appropriate washout of SSc-ILD medications other than MMF by time of study screening. For such patients, there must be no plan to start SSc-ILD medication during the study.

b. Taking background MMF

Participant is taking background MMF (≤1.5 g twice daily), and the dose has been stable during the 3 months before study Day 1.

8.1.3 Informed Consent and Protocol Adherence:

9. Able to understand and sign a written informed consent form
10. Able to understand the importance of adhering to study treatment and the study protocol, and willing and able to follow all study requirements, including the concomitant medication restrictions, throughout the study
11. Use of effective contraception:
Women of childbearing potential are required to have a negative pregnancy test before treatment and must agree to maintain highly effective contraception by practicing abstinence or by using at least two methods of birth control from the date of providing written informed consent through the end of the study (see 14.0 Pregnancy). The six participants enrolled in the study group already using mycophenolate background medication will have been previously counseled as found clinically indicated on the use of IUD mechanical contraception, as mycophenolate interferes with effectiveness of hormonal contraceptives. The six participants enrolled in the study group not using background mycophenolate, if not abstinent, will be required to be using an oral contraceptive or an IUD as one

of the two methods for birth control. The additional use of a spermicide or other standard means of contraception is acceptable in both study groups.

12. Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following (see 14.0 Pregnancy):
    - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.

8.2 Exclusion Criteria

Patients who meet any of the following criteria are not eligible to participate in the study:

8.2.1 Disease-Related Exclusions:

1. Clinically significant pulmonary hypertension, based on any of the following criteria:
    a. Receiving treatment for pulmonary arterial hypertension, or
    b. Evidence for any form of pulmonary hypertension as determined by previous right heart catheterization. Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure ≥ 20 mmHg at rest, a mean pulmonary capillary wedge pressure ≤ 15 mmHg, and the pulmonary vascular resistance ≥ 3 Wood units, or
    c. Resting transthoracic echocardiography within 6 months of providing written informed consent reporting an estimated right ventricular systolic pressure of >40 mm Hg if subsequent confirmatory right heart catheterization has not been done.

2. Resting transthoracic echocardiography within 6 months of providing written informed consent showing evidence of right atrial or right ventricular enlargement or significant left ventricular dysfunction with left ventricular ejection fraction < 40%

3. Clinical evidence of significant aspiration or uncontrolled gastroesophageal reflux (University of California, Los Angeles, Scleroderma Clinical Trial Consortium Gastrointestinal Tract multi-item scale, 2.0 [UCLA SCTC GIT 2.0] reflux domain score >2.00) [148, 149]

4. Known esophageal dysfunction with esophageal stricture sufficient to limit the ability to swallow oral medication

5. Clinical evidence of significant gastrointestinal involvement (UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract multi-item scale 2.0 [UCLA SCTC GIT 2.0] distention/bloating, diarrhea, or social function domain scores >2.00) [148, 149], or evidence of malabsorption.

6. Prior history of renal crisis

8.2.2 Medical Exclusions:

7. Features supporting diagnosis of another connective-tissue disorder (e.g., rheumatoid arthritis or systemic lupus erythematous)
8. Features supporting diagnosis of another pulmonary disorder (e.g., chronic obstructive pulmonary disease, emphysema, clinically significant adult asthma, or cancer)
9. Clinical evidence of active infection including, but not limited to, bronchitis, pneumonia, sinusitis, or urinary tract infection.
10. History of a clinically significant environmental exposure that is known to cause pulmonary fibrosis including, but not limited to, drugs (e.g., amiodarone), asbestos, beryllium, radiation, or domestic birds or other exposures associated with hypersensitivity pneumonitis
11. Tobacco smoking within 3 months of screening or unwillingness to avoid smoking throughout the study (e.g., cigarette, pipe, or cigar)
12. History of unstable or deteriorating cardiac disease within the previous 6 months relative to study Day 1 including, but not limited to, the following:
    a. Unstable angina pectoris
    b. Myocardial infarction
    c. Congestive heart failure requiring hospitalization
    d. Uncontrolled clinically significant arrhythmia
    e. Clinically significant pericardial effusion
    f. Pulmonary hypertension (see 8.2.1 Exclusion Criteria - Disease Related)
13. Known underlying liver disease (e.g., hepatitis or cirrhosis)
14. Known or suspected peptic ulcer
15. Known active hematologic disorder other than anemia of chronic disease or iron deficiency anemia (hemoglobin < 8.0 gm/dl).
16. Known hematologic malignancy
17. History of any malignancy within the last 5 years other than non-melanoma skin cell cancers cured by local resection or carcinoma-in-situ
18. Prior stem cell or bone marrow transplant
19. Any condition that might be significantly exacerbated by the known side effects associated with ixazomib including known ≥ grade 2 peripheral neuropathy
20. Pregnancy or lactation: Positive pregnancy test; currently lactating; or for women of childbearing potential and men, an unwillingness to maintain abstinence or highly effective contraception (see 8.1.3 Eligibility Criteria – Informed Consent and Protocol Adherence)

21. History of alcohol or substance abuse in the previous 2 years relative to study Day 1.

22. Expected to have study participation interrupted for a foreseeable medical or surgical event (e.g., organ, stem cell, or bone marrow transplant; orthopedic-related surgery).

23. Any condition that is likely to result in the death of the patient within 12 months.

24. History of known or active COVID19 infection.

8.2.3 Laboratory Exclusions:

25. Any of the following screening test criteria:
    a. Hemoglobin ≤ 8.0 gm/dl
    b. Absolute neutrophil count ≤ 1000
    c. Platelet count ≤ 75,000
    d. Total bilirubin above 1.5 x upper limit of the normal range (ULN), except in patients with predominantly unconjugated hyperbilirubinemia (e.g., Gilbert's syndrome)
    e. Aspartate or alanine aminotransferase (AST or ALT) >2 × ULN
    f. Alkaline phosphatase >2 × ULN
    g. Creatinine clearance <30 mL/min

8.2.4 Medication Exclusions:

26. Any prior use of ixazomib or other proteasome inhibitor

27. Any prior use of rituximab

28. Any prior use of cyclophosphamide

29. Suspected intolerance, allergy, or hypersensitivity to ixazomib or any of its excipients

30. Ongoing use or expected use of any of the following therapies:
    a. Investigational drug within the 28 days before screening (an investigational drug is defined as any drug that has not been FDA approved for marketing)
    b. Strong CYP3A inducers (e.g. rifampin, rifapentine, rifabutin, carbamazepine, enzalutamide, phenytoin, fosphenytoin, phenobarbital, St. John's wort)
    c. Methotrexate
    d. Leflunomide
    e. Azathioprine
    f. Sirolimus
    g. Tacrolimus
    h. Oral corticosteroids at a dose >10 mg/d prednisone equivalent
    i. D-penicillamine
    j. Minocycline
    k. Interferon-γ

l. Endothelin-1 receptor antagonists (e.g., bosentan, ambrisentan or macitentan)
m. Phosphodiesterase inhibitors (for use other than erectile dysfunction or Raynaud's phenomenon)
n. Riociguat
o. Tumor necrosis factor-α (TNF-α) inhibitor drugs
p. Tocilizumab
q. Rituximab
r. Abatacept
s. Cyclosporine
t. Cyclophosphamide
u. Intravenous immunoglobulin (IVIG)
v. Nintedanib

8.2.5 General Exclusion:

31. Unsuitable for enrollment or unlikely to comply with study requirements, as assessed by the investigator

9.0 STUDY TREATMENT

9.1 Ixazomib Dosing Regimen, Administration, and Handling

Ixazomib will be supplied by Takeda as capsules of 2.3mg, 3mg, and 4.0 mg. All patients will be given oral ixazomib during the study. The dosing will be 4 mg orally on days 1, 8, and 15 of a 28-day treatment cycle for 6 cycles. The first dose of ixazomib will be taken on study Day 1.

9.1.1 Dosing Guidelines:

- Each dose is to be taken at the same time of day.
- Dosing should be 1 hour before or at least 2 hours after food.
- The capsule is to be swallowed whole with a total of approximately 8 ounces (240 mL) of water; it should not be opened, crushed, or chewed.
- A missed dose should be taken only if the next scheduled dose is at least 72 hours away; otherwise, the missed dose is to be skipped and participant instructed to take the next scheduled dose.
- A repeat dose should not be taken if vomiting occurs; the participant is to continue therapy with next scheduled dose.

9.1.2 Precautionary Measures:

- As Ixazomib is cytotoxic, direct contact with capsule contents is to be avoided. Study participants will use single gloves when handling intact capsules.
- If capsule breakage occurs, study participants should avoid direct contact of contents with the skin or eyes. If contact occurs with the skin, it should be washed thoroughly with soap and water. If contact occurs with the eyes, they should be flushed thoroughly with water.
- Dispose properly any unused medicinal product or waste material.

- Participants who have some symptoms of gastroesophageal reflux but do not meet the disease-related exclusion criterion can be enrolled, but will be advised on ways to manage the symptoms with life-style changes (e.g., avoid reclining after a meal, not eating within 3 hours of retiring at night, elevate the head of the bed 4-6 inches, and avoidance certain foods). Any medication required to manage GI reflux/symptoms will be commenced before the start of ixazomib treatment on study Day 1.

9.2 Ixazomib Dose Modification or Interruption

9.2.1 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with ixazomib treatment. Further details of management of ixazomib AEs are described in the ixazomib IB [143].

Ixazomib dose modification or interruption will be allowed for safety or tolerability reasons at any time during the study at the discretion of the investigator. In general, if dose modification is necessary, the first ixazomib dose reduction is to 3 mg; second dose reduction is to 2.3 mg; and thereafter, to discontinue use.

9.2.2 Hematologic toxicity

9.2.2.1 In the event of absolute neutrophil count ≤ 1000/ mm^3, ixazomib dose will be managed as follows:

1. Ixazomib administration will be interrupted and paused until the absolute neutrophil count (ANC) is > 1000 / mm^3 upon retesting of the CBC weekly or sooner as clinically indicated.
2. G-CSF administration may be considered as clinically indicated.
3. Upon recovery of the ANC > 1000/ mm^3, ixazomib administration may resume at the first reduction dose of 3 mg with weekly monitoring of CBC for the remainder of that study cycle until the next study visit. The 3 mg dose should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless recurrent ANC ≤ 1000/ mm^3 occurs.
4. In that instance, ixazomib administration will be interrupted and paused until the ANC has recovered > 1000/ mm^3 upon retesting of the CBC weekly or sooner as clinically indicated.
5. G-CSF administration may be considered again as clinically indicated.
6. Upon recovery of the ANC > 1000/ mm^3, ixazomib administration may resume at the second reduction dose of 2.3 mg with weekly monitoring of CBC for the remainder of that study cycle until the next study visit. The 2.3 mg dose should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless recurrent ANC ≤ 1000/ mm^3 occurs.
7. In that instance, ixazomib administration will be discontinued. A CBC will be monitored weekly or sooner if clinically indicated until the ANC has recovered to > 1000/ mm^3. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

9.2.2.2 In the event of platelet count ≤ 30,000 mm^3, ixazomib dose will be managed as follows:

- **If thrombocytopenia is asymptomatic or associated with petechiae/bruising without other significant bleeding**:
    1. Ixazomib administration will be interrupted and paused until the platelet count is ≥ 50,000/mm^3 upon retesting of the CBC daily and then weekly until the platelet count is ≥ 75,000/mm^3 .
    2. Upon recovery of the platelets ≥ 75,000/mm^3 ixazomib administration may resume at the first reduction dose of 3 mg with weekly monitoring of CBC for the remainder of that study cycle until the next study visit. The 3 mg dose should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless recurrent thrombocytopenia ≤ 30,000/ mm^3 occurs.
    3. In that instance, if thrombocytopenia is asymptomatic or associated with petechiae /bruising without other significant bleeding, ixazomib administration will be interrupted and paused until the platelet count is ≥ 50,000/mm^3 upon retesting of the CBC daily and then weekly until the platelet count is ≥ 75,000/mm^3 .
    4. Upon recovery of the platelets ≥ 75,000/mm^3, ixazomib administration may resume at the second reduction dose of 2.3 mg with weekly monitoring of CBC for the remainder of that study cycle until the next study visit. The 2.3 mg dose should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless recurrent thrombocytopenia ≤ 30,000/ mm^3 occurs.
    5. In that instance, ixazomib administration will be discontinued. If thrombocytopenia is asymptomatic or associated with petechiae/ bruising without other significant bleeding, the thrombocytopenia will be monitored with a CBC daily until the platelet count is ≥ 50,000/mm^3 and then weekly until the platelet count has returned to ≥ 75,000/mm^3. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

9.2.3 Non-Hematologic toxicity:

9.2.3.1 In the event of either new or worsening baseline peripheral neuropathy, ixazomib dose will be managed as follows:

- **If grade 1 (mild) new peripheral neuropathy with pain or worsening baseline peripheral neuropathy grade 2 (moderate):**
    1. Ixazomib administration will be interrupted and paused until the peripheral neuropathy is grade 1 or lower without pain, or at patient's baseline.
    2. If recovery of the neuropathy has occurred, ixazomib administration may resume at the first reduction dose of 3 mg and should follow the dosecycle schedule for the remainder of that study visit and subsequent study visits unless recurrent worsening neuropathy occurs.
    3. In that instance, if return of grade 1 peripheral neuropathy with pain or worsening again of baseline peripheral neuropathy grade 2, ixazomib

administration will be interrupted and paused until the peripheral neuropathy is grade 1 or lower without pain, or at patient's baseline.
4. If improvement of the neuropathy has occurred, ixazomib administration may resume at the second reduction dose of 2.3 mg and should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless any recurrent or worsening of baseline neuropathy occurs.
5. In that instance, ixazomib administration will be discontinued. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

- **If grade 2 (moderate) new peripheral neuropathy with pain**
    1. Ixazomib administration will be interrupted and paused until the peripheral neuropathy is grade 1 or lower without pain, or at patient's baseline.
    2. If improvement of the neuropathy has occurred, ixazomib administration may resume at the first reduction dose of 3 mg and should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless recurrent worsening neuropathy occurs.
    3. In that instance, if return of grade 2 peripheral neuropathy with pain, ixazomib administration will be interrupted and paused until the peripheral neuropathy is grade 1 or lower without pain, or at patient's baseline.
    4. If improvement of the neuropathy has occurred, ixazomib administration may resume at the second reduction dose of 2.3 mg and should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless any recurrent or worsening of baseline neuropathy occurs.
    5. In that instance, ixazomib administration will be discontinued. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

- **If grade 3 (severe) new peripheral neuropathy with pain or worseningbaseline peripheral neuropathy to grade 3 (severe)**
    1. Ixazomib administration will be discontinued. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

9.2.3.2 In the event of either new or worsening rash, ixazomib dose will be managed as follows:

- **If new grade 1 (mild) or 2 (moderate) rash for which there is no other immediate explanation** ixazomib dose will be managed as follows:
    1. Ixazomib administration will be interrupted and paused until the rash is grade improved grade 1 or resolved if grade 1.
    2. Upon improvement of the rash, ixazomib administration may resume at the first reduction dose of 3 mg and should follow the dose cycle schedule forthe

remainder of that study visit and subsequent study visits unless recurrent rash grade 2 occurs.

3. In that instance, ixazomib administration will be interrupted and paused until the rash is improved grade 1 or resolved if grade 1.
4. Upon improvement of the rash, ixazomib administration may resume at the second dose reduction dose of 2.3 mg and should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless recurrent rash grade 2 occurs.
5. In that instance, ixazomib administration will be discontinued. The participant will be monitored until the rash is improved grade 1 or resolved. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

- **If grade 3 (severe) rash for which there is no other immediate explanation** ixazomib dose will be managed as follows:
    1. Ixazomib administration will be discontinued. The participant will be monitored until the rash is improved grade 1 or resolved. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

9.2.3.3 In the event of hepatic impairment ixazomib dose will be managed as follows:

- If serum alkaline phosphatase is not more than 2 X upper limited of normal (ULN); total bilirubin is not greater than 1.5 X ULN except in patients with predominantly unconjugated hyperbilirubinemia (e.g., Gilbert's syndrome), and AST or ALT is not more than 2 X ULN, ixazomib dose will be managed as follows:
    1. Ixazomib administration will be revised to the first reduction dose of 3 mg and should follow the dose cycle schedule for the remainder of that study visit with weekly monitoring of alkaline phosphatase, total and indirect bilirubin, and AST or ALT for the remainder of that study cycle until the next study visit. The 3 mg dose should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless worsening of liver function tests is observed.
- If serum alkaline phosphatase is greater than 2 X upper limited of normal (ULN), total bilirubin is greater than 1.5 X ULN except in patients with predominantly unconjugated hyperbilirubinemia (e.g., Gilbert's syndrome), and AST or ALT is more than 2 X ULN, ixazomib dose will be managed as follows:
    1. Ixazomib administration will be discontinued. The participant will be monitored weekly until the liver function tests return to baseline or resolve. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

9.2.3.4 If other nonhematologic adverse events, grade 2 or 3, ixazomib dose will be managed as follows:

1. Ixazomib administration will be interrupted and paused until the adverse event has improved to grade 1 or resolved.

2. Supportive care for the adverse event may be considered as clinically indicated.
3. Upon improvement of the adverse event to grade 1 or resolution, ixazomib administration may resume at the first reduction dose of 3 mg and should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless a recurrent adverse event grade 2 or 3 of the same nature occurs.
4. In that instance, ixazomib administration will be interrupted and paused until the adverse event has improved to grade 1 or resolved.
5. Upon improvement of the adverse event to grade 1 or resolution, ixazomib administration may resume at the second reduction dose of 2.3 mg and should follow the dose cycle schedule for the remainder of that study visit and subsequent study visits unless a recurrent adverse event grade 2 or 3 of the same nature occurs.
6. In that instance, ixazomib administration will be discontinued. Supportive care for the adverse event may be considered as clinically indicated. The participant will be discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).

If participants require hospitalization, consideration will be given to continuing study treatment, if appropriate. If the participant is hospitalized at an institution other than Mayo Clinic Hospital, the treating physician will be encouraged to discuss the patient's management with a Mayo investigator at the earliest possible time. All records pertaining to the hospitalization will be obtained.

9.3 Restarting Ixazomib

Whether ixazomib can be restarted after a treatment interruption will depend on reason for the interruption; and if an adverse event (AE) its severity and its duration.

9.3.1 Interruption ≤28 Days:

- Ixazomib treatment can be restarted with dose modification as specified according to the type of adverse event. Dose up-titration back to ixazomib doses used during prior cycles associated with an adverse event will not be permitted.

9.3.2 Interruption >28 Days:

- **For an AE:** Treatment cannot be restarted after an interruption of >28 days because of a persisting AE. Ixazomib will be permanently discontinued, and the patient discontinued from the study and will proceed to complete assessments and procedures for early discontinuation (See 15.0 Early Discontinuation).
- **For Other Reasons:** If treatment is interrupted for >28 days for any other reason, ixazomib treatment can be restarted at the discretion of the investigator. If treatment is restarted, the ixazomib dose will be the most recent dose level being used prior to the interruption.

After restarting therapy, study visits will continue to be scheduled relative to Day 1 of study participation. The total study duration will be 28-29 weeks, starting with Day 1, and if dosing is interrupted, the study duration will remain unchanged.

9.4 Ixazomib Supply

Ixazomib 4 mg, 3mg, and 2.3 mg capsules are being supplied by Takeda.

Ixazomib will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

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

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 at room temperature (2°C to 30°C). Ensure that the drug is used before the retest expiry date provided by Takeda. 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 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 at room temperature (2°C to 30°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.

9.5 Dispensing of Ixazomib

Beginning on study on Day 1, and at each subsequent study visit, a 4-week supply (3 doses) of ixazomib will be dispensed to the participant for consumption during the next 28 day cycle. The day 1 dose for that cycle will be observed taken by a member of the study team during at the time of dispensing. Participants will be instructed to store day 8 and day 15 ixazomib doses at room temperature not to exceed 30°C /86°F and to return all used and unused capsules of ixazomib.

9.6 Ixazomib Accountability

The monitoring of the ixazomib inventory may be delegated to the responsible pharmacist; however, the investigator will be ultimately responsible for monitoring of the inventory. Ixazomib will not be used for any purpose other than that described in the protocol, and it will be stored in a secure place with access restricted to authorized personnel.

Participants will return all used and unused capsules of ixazomib at each study visit.

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

10.0 BACKGROUND MEDICATION MMF

The study will enroll participants who either are not on background SSc-ILD medication or are on a background stable dose of MMF (see Study Population 8.1.2 SSc and SSc-ILD Related Criteria). MMF will be treated as background medication and will continue to be prescribed as part of usual clinical care. MMF will not be provided as part of the study. Participants on MMF will continue to take MMF during the study. Background MMF cannot be switched to another agent, nor is the addition of other background medications permitted; if this is necessary, the patient will be discontinued from the study and will procced to complete early discontinuation assessments and procedures. Changes in the dose of the background MMF are not planned during the study; but if patient management requires a dose adjustment within the established limits of MMF ≤1.5 g BID, the patient will remain in the study. Changes within the allowable dose range of MMF will not be considered a deviation. MMF can produce significant adverse effects, including effects on the GI system, skin, liver, and central nervous system. Participants will be monitored for adverse effects of MMF when being used concurrently with ixazomib.

11.0 OTHER PRIOR THERAPIES

Any prior use of ixazomib or other proteasome inhibitor, rituximab, or oral or intravenous cyclophosphamide will exclude participation in this study (See 8.2.4 Eligibility Criteria Medication Exclusions).

Patients wishing to participate who are taking medications specifically for SSc-ILD other than MMF or any other excluded medication (see 8.2.4 Eligibility Criteria Medication Exclusions) will be required to discontinue that medication and undergo medication washout (See Study Assessments By Visit 18.1 – Washout Period). After completing medication washout, the participant can be screened for study eligibility.

Bronchodilator use will be prohibited in the 24 hours before pulmonary function testing and ECG tests throughout the study.

12.0 CONCOMITANT THERAPIES

Concomitant therapies are any therapies used from the time that informed consent is obtained the day of the last study visit. Therapies that are considered necessary for the patient's welfare may be given at the discretion of the investigator, with careful monitoring for new signs or symptoms. All the following will be considered concomitant medications and will be recorded at each study visit:

- Prescription drugs
- Over-the-counter drugs (e.g., antacids or eye drops)
- Vitamins, herbal preparations, dietary supplements, and homeopathic preparations
- Prohibited drugs (See 13. 0 Prohibited Therapies)

Oral corticosteroids are used with caution in scleroderma because of their potential for triggering SSc renal crisis if corticosteroid dose equivalents of > 15 mg/day prednisone are used. However, oral corticosteroids will be permitted if clinically indicated during the study, provided the dose does not exceed the equivalent of prednisone 10 mg/day.

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. Intravenous fluids should be given to prevent volume depletion.
- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice. Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Antiviral therapy such as acyclovir may be administered if medically appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

Participants will be monitored for any adverse effects related to concomitant therapies used concurrently with ixazomib.

13.0 PROHIBITED THERAPIES

Medications listed in 8.2.4 Eligibility Criteria Medication Exclusions are additionally prohibited during participation in this study. If a participant receives any of these prohibited therapies, the therapies will be recorded, and the participant will be discontinued from the study. The participant will proceed to complete early discontinuation assessments and procedures (see 15.0 Early Discontinuation).

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

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

- If use of one of these CYP3A inducing medications is required, the participant will be discontinued from the study. The participant will proceed to complete early discontinuation assessments and procedures.

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

- Excluded foods and dietary supplements include St. John's wort.
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day.

14.0 PREGNANCY

It is not known what effects ixazomib has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

14.1 Female patients

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days after the last dose of study drug (See 8.1.3 Study Population Informed Consent and Protocol Adherence), or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

14.2 Male patients

Male patients even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug (See 8.1.3 Study Population Informed Consent and Protocol Adherence), or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

15.0 EARLY DISCONTINUATION

Patients will be free to discontinue their participation in the study at any time and without prejudice to further treatment. In addition, patients will permanently discontinue study

drug and will be discontinued from study for any of the following reasons:

- Unacceptable toxicity
- Interruption of study treatment for >28 days because of an AE(s)
- Patients who were on no background SSc-ILD medication at study entry and need to begin a SSc-ILD medication:
    - A decline of FVC by ≥15% predicted or a decline of DLC0 by ≥ 15% predicted observed during the study that is sustained 4 weeks, or a decline of FVC itself to <45% predicted or decline of DLCO itself to <40% predicted observed during the study and if not explained by alternative etiology other than worsening scleroderma-related ILD as confirmed by HRCT chest scan will be considered meaningful differences in regards to the participant's background pulmonary status. In such an event, the patient will be discontinued from the study and will proceed to complete early discontinuation assessments and procedures.
- Patients on background MMF at study entry who need either (1) to switch to another background SSc-ILD medication, or (2) to begin additional treatment with another background SSc-ILD medication:
    - A decline of FVC by ≥15% predicted or a decline of DLC0 by ≥ 15% predicted observed during the study that is sustained 4 weeks, or a decline of FVC itself to <45% predicted or decline of DLCO itself to <40% predicted observed during the study and if not explained by alternative etiology other than worsening scleroderma-related ILD as confirmed by HRCT chest scan will be considered meaningful differences in regards to the participant's background pulmonary status. In such an event, background MMF may not be switched to another agent in the study nor is the addition of other background medication permitted in the study; if this is necessary, the patient will be discontinued from the study and will proceed to complete early discontinuation assessments and procedures.
- Need for a prohibited medication
- Pregnancy
- Organ, stem cell, or bone marrow transplant
- At the discretion of the investigator

For participants taking no background SSc-ILD medication at study entry who need to begin a SSc-ILD medication and participants on background MMF at study entry who need either (1) to switch to another background SSc-ILD medication, or (2) to begin additional treatment with another background SSc-ILD medication, the new SSc-ILD medication will be prescribed as routine clinical care and will not be provided as part of the study.

Participants who prematurely and permanently discontinue ixazomib study treatment will return to the clinic as soon as possible after the last dose of ixazomib and not later than 10 days after that dose to complete early discontinuation assessments and procedures as planned for study day 168 (week 24) office visit (see 18.3.10).

Participants who prematurely and permanently discontinue ixazomib study treatment will

again return to the clinic 28-35 days after completing the study early discontinuation assessments and procedures visit to complete early discontinuation assessments and procedures as planned for study post-treatment follow-up day 196-203 (week 28-29) office visit (see 18.3.11).

Any patient who prematurely and permanently discontinues ixazomib study treatment will be discontinued from the study and will be encouraged to continue post-discontinuation monitoring if eligible to do so.

15.1 POST-DISCONTINUATION MONITORING FOR SAFETY AND EFFICACY OBJECTIVES

15.1.1 Eligibility for Post-Discontinuation Monitoring for Safety and Efficacy Objectives

Participants who have prematurely and permanently discontinued ixazomib study medication for any of the following reasons will be encouraged to continue monitoring for safety and efficacy objectives:

- Unacceptable toxicity
- Interruption of study treatment for >28 days because of an AE(s)
- Patients who were on no background SSc-ILD medication at study entry and need to begin a SSc-ILD medication
- Patients on background MMF at study entry who need either (1) to switch to another background SSc-ILD medication, or (2) to begin additional treatment with another background SSc-ILD medication
- Need for a prohibited medication
- At the discretion of the investigator

15.1.2 Post-Discontinuation Monitoring Visits

Based on the date of completion of the early discontinuation assessments and procedures as planned for study day 168 (week 24), eligible participants will continue to be monitored and evaluated subsequently every 28 days (± 4days) for safety and efficacy objectives. Participants initiating post-discontinuation monitoring visits will not complete the study early follow-up office visit (day 196-203) assessments and procedures (see 15.0).

15.1.3 Post-Discontinuation (PD) Monitoring Visit 1 (PD day 28 ± 4 days), Visit 2 (PD day 56 ± 4 days), Visit 4 (PD day 112 ± 4 days), and Visit 5 (PD day 140 ± 4 days) as necessary

Post-discontinuation monitoring visits PD Visit 1, PD Visit 2, PD Visit 4, and PD Visit 5 as necessary will include the following assessments and procedures:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. UCLA SCTC GIT 2.0 questionnaire
4. Hematology and serum chemistries blood samples
5. Clinical Immunology Tests blood sample
6. Blood sample for biomarker analyses
7. Spirometry and DLCO

15.1.4 Post-Discontinuation Visit 3 (PD day 84 ± 4 days) and Post-Discontinuation Visit 6 (PD day 168 ± 4 days) as necessary

Post-discontinuation visits PD Visit 3 and PD Visit 6 as necessary will include following assessments and procedures:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, andrespiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PtGA
7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample
10. Blood sample for biomarker analyses
11. Complete pulmonary function tests including lung volumes and DLC0 % predicted

15.1.5 Final Post-Discontinuation Visit

Regardless of the number of post-discontinuation visits needed every 28 day ± 4 days following the date of completion of the early discontinuation assessments and procedures as planned for study day 168 (week 24), the final post-discontinuation visit will occur at a time point between what would have been study day visit 168 and study day 196-203 follow-up office visit should the participant have not prematurely discontinued ixazomib study medication. The final post-discontinuation visit will include following assessments and procedures:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PtGA

7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample
10. Blood sample for biomarker analyses
11. Complete pulmonary function tests including lung volumes and DLC0 % predicted
12. HRCT chest scan

16.0 STUDY ASSESSMENTS

16.1 Assessments for Safety and Tolerability

Safety outcome measures used will include, but will not be limited to:

- Treatment-emergent AEs
- Treatment-emergent SAEs
- Treatment-emergent treatment-related AEs
- Treatment-emergent treatment-related SAEs
- Treatment-emergent AEs leading to ixazomib dose modifications
- Treatment-emergent AEs leading to early discontinuation of ixazomib
- Treatment-emergent changes in clinical laboratory measures
- Treatment emergent changes in patient vital signs
- Treatment emergent changes in UCLA SCTC GIT 2.0 questionnaire

16.2 Assessments for Clinical Efficacy

16.2.1 ACR CRISS (American College of Rheumatology Composite Response Index for clinical trials in early diffuse cutaneous Systemic Sclerosis) [150]

16.2.2 Additional Assessments for Clinical Efficacy

Additional assessments for clinical efficacy will include:

1. Each of the five individual components of ACR CRISS: mRSS (modified Rodnan skin score), FVC % predicted, HAQ-DI (Health Assessment Questionnaire-Disability Index), PtGA (Patient Global Assessment), MDGA (Physician Global Assessment)
2. DLCO % predicted
3. HRCT chest scan ILD severity using the Goh scoring method [6].
4. Additional patient reported outcome Mahler Baseline/Transitional Dyspnea Index (Mahler BDI/TDI).

17.0 DESCRIPTION OF STUDY MEASURES USED FOR ASSESSMENTS

17.1 Informed Consent

Informed consent will be obtained before any study-related observations, assessments, or procedures take place. For patients who require medication washout, informed consent will be obtained before the start of washout. For patients who do not require medication washout, informed consent will be obtained at the screening visit before any study related assessments or procedures are performed. The results of all study assessments and procedures will be documented in the patient's medical record and recorded for study purposes. Study assessments and procedures to be included with each study visit are described in Section 18.1 Study Assessments by Visit. Study assessments and procedures

to be included with each extension study visit are described in Section 25.2 Extension Study Assessments by Visit.

17.2 Study Measures for the Primary Objective to Assess the Safety and Tolerability of Ixazomib:

17.2.1 Medical History

A complete medical history will include a review of all body systems pertinent to the participant, as well as prior and concomitant medications. A complete medical history will be obtained at the start of the medication washout for participants who require washout because of excluded medications, or during the screening for patients who do not require medication washout. A directed medical history will include a review of AEs/SAEs and concomitant medications that have been taken since the preceding visit. A directed medical history will be performed at screening for participants who go through a medication washout period, at study day 1, and at each subsequent study visit every 28 days (weeks 4-24) and at the concluding follow-up office visit (week 28-29) for participants not proceeding on to the extension study. For the extension study, a directed medical history will be performed at each study visit every 28 days (weeks 24-48) and at the concluding follow-up study day 196-203 (week 52-53) office visit.

17.2.2 Physical Examination and Vital Signs

Physical examinations will include a review of all body systems pertinent to the patient, body weight (in kilograms), and vital signs (blood pressure, heart rate and respiratory rate). Height (in centimeters) will also be measured as part of the physical examination at the screening visit. A physical examination will be subsequently performed at study day 1, at study day 84 (week 12), day 168 (week 24), and at the concluding follow-up study day 196-203 (week 28-29) office visits for participants not proceeding on to the extension study. For the extension study, a physical examination will be performed at study day 84 (week 36), day 168 (week 48), and at the concluding follow-up study day 196-203 (week 52-53) office visits.

If clinically significant abnormalities are observed before or on study Day 1, they will be reported in the patient's medical history. If clinically significant abnormalities are observedafter study Day 1, a determination will be made if they are new AEs.

17.2.3 Clinical Laboratory Tests

All clinical laboratory tests will be performed by Mayo Clinic Laboratory:

- **Hematology:** complete blood cell count with automated differential and platelet count, erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP).
- **Serum Chemistry:** albumin, alkaline phosphatase, ALT, AST, bicarbonate, direct bilirubin, indirect bilirubin, total bilirubin, calcium, cholesterol, chloride, creatine kinase (CK), creatinine, triglycerides, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, total protein, sodium, urea nitrogen, and uricacid.
- **Clinical Immunology:** serum protein immunoelectrophoresis, quantitative immunoglobulins (IgG, IgA, IgM), and IgG tetanus toxoid titer.

The hematology, serum chemistry, and clinical immunology lab tests will be obtained at screening, study day 1, day 28 (week 4), day 56 (week 8), day 84 (week 12), day 112 (week 16), day 140 (week 20), day 168 (week 24), and at the concluding follow-up study day 196-203 (week 28-29) office visits for participants not proceeding on to the extension study.

Additional lab visits are scheduled day 14 (week 2), day 42 (week 6), and day 70 (week 10) for monitoring hematology and serum chemistry tests between study office visits during the first three ixazomib cycles. For the extension study, hematology and serum chemistry tests will be obtained at study day 28 (week 28), day 56 (week 32), day 84 (week 36), day 112 (week 40), day 140 (week 44), day 168 (week 48), and at the concluding follow-up study day 196-203 (week 52-53) office visits.

Specified clinical laboratory assessments will be obtained more frequently if clinically indicated and in conjunction with other laboratory assessments as required.

- **Pregnancy Test** (women of childbearing potential): serum pregnancy test will be performed at screening, on study Day 1; day 28 (week 4), day 56 (week 8), day 84 (week 12), day 112 (week 16), day 140 (week 20), day 168 (week 24), and day 196-203 (week 28-29) follow-up visit for participants not proceeding on to the extension study. For the extension study, serum pregnancy test will be obtained at study day 28 (week 28), day 56 (week 32), day 84 (week 36), day 112 (week 40), day 140 (week 44), day 168 (week 48), and at the concluding follow-up study day 196-203 (week 52-53) office visits.

17.2.4 12-Lead Electrocardiogram

A 12-lead ECG with a rhythm strip will be done during screening. Bronchodilator use will be prohibited in the 24 hours before ECG testing.

17.2.5 Echocardiogram

If a resting transthoracic echocardiogram has not been done within 6 months prior to written informed consent at medication washout or screening, as applicable, it will be performed at screening.

17.2.6 University of California, Los Angeles, Scleroderma Clinical Trials Consortium Gastrointestinal Scale, 2.0, Questionnaire [148, 149]

The UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract (UCLA SCTC GIT) 2.0 is a self-administered survey. The survey consists of 34 questions (Reflux 1 to 8, Distention/Bloating 9 to 12, Fecal Soilage 13, Diarrhea 14 to 15, Social functioning 16 to 21, Emotional well-being 22 to 30, Constipation 31 to 34). The items are scored on a scale from 0 to 3, where 0 indicates better health and 3 indicates worse health, except for questions 15 and 31, which are scored as 0 (better health) and 1 (worse health). Scores from all scales except the constipation scale are averaged to form a total GIT score from 0 (no gastrointestinal problems) to 3 (most severe) that captures overall burden of severity of SSc-associated GIT involvement.

The UCLA SCTC GIT 2.0 questionnaire will be used to obtain the participant's assessment of

the frequency of GI symptoms in the preceding 7 days and how those symptoms affected his/her life. The questionnaire will be administered during screening (see 8.2.1 Study Population Exclusion Criteria), at study Day 1, and at each subsequent study visit every 28 days (weeks 4-24). For the extension study, the questionnaire will be administered at study day 84 (week 36) and study day 168 (week 48) office visits.

17.3 Study Measures for the Secondary Objective to Assess the Clinical Efficacy of Ixazomib

17.3.1 High-Resolution Computed Tomography Scan

An HRCT chest scan will be used at screening to confirm eligibility. A HRCT chest scan may be used for this purpose if completed within 3 months prior to the date of written informed consent at either medication washout or screening, as applicable. The HRCT must demonstrate features consistent with SSc-ILD as confirmed by review of the HRCT images by Mayo radiology study staff. If the previous HRCT chest study is determined to be technically inadequate or cannot be made available for review by Mayo radiology study staff, or if the HRCT chest scan was performed more than 3 months prior to signing of written informed consent, a HRCT chest scan will be obtained during study screening. The extent of scleroderma lung involvement identified on the HRCT study, limited or extensive, will be scored according to the Goh criteria [6]. A follow-up HRCT chest scan will be obtained at the study visit on day 168 (week 24). For the extension study, HRCT chest scan will be obtained at study day 168 (week 48).

17.3.2 Pulmonary function testing, Spirometry, and DLCO Measurements

All equipment, procedures, and personnel qualifications for the assessment of lung function are based on the recommendations of the American Thoracic Society/ European Respiratory Society. Complete pulmonary function testing includes lung volumes and DLCO. Spirometry includes total lung capacity (TLC), forced expiratory volume in 1 second [FEV1] and FVC % predicted; DLCO measurements also will be obtained. Bronchodilator use will be prohibited in the 24 hours before spirometry testing. Complete pulmonary function tests will be obtained at screening; study visit day 84 (week 12) and study visit day 168 (week 24). Spirometry and DLCO will be obtained at study visit day 28 (week 4), day 56 (week 8), day 112 (week 16), and day 140 (week 20). For the extension study, complete pulmonary function will be obtained at study day 84 (week 36) and study day 168 (week 48).

17.3.3 Disease-Status Scales

The following disease-status scales will be used to obtain the participant's evaluation of the symptoms of SSc and SSc-ILD and/or the effect of those symptoms on his/her quality of life:

- **Mahler Baseline/Transitional Dyspnea Index** (Mahler BDI/TDI): patient's assessment of the severity of dyspnea.
- **Scleroderma Health Assessment Questionnaire** (SHAQ): patient's assessment of how the disease affects his or her ability to function in daily life in the eight domains of the Health Assessment Questionnaire Disability Index (HAQ-DI). These domains include dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities, along with a visual analog scale (VAS) rating pain severity;

SHAQ additionally includes five scleroderma−specific VAS scales related to Raynaud's, digital fingertip ulcers, gastrointestinal symptoms, lung symptoms/shortness of breath, and patient overall disease severity assessment.

- **Patient Global Assessment of Disease Activity** (PtGA): Patient's Global Assessment is a patient-reported outcome that represents the subject's overall assessment of his orher current health (Question- how was your overall health in the last week) on a 11- point Numeric rating scale anchored at 0 (excellent) to 10 (extremely poor), with higher scores indicating worse disease in terms of severity, damage, or overall disease.

The disease-status scales will be completed at study Day 1, day 84 (week 12) and day 168 (week 24) but will administered more frequently if clinically indicated. For the extension study, the disease-status scales will be completed at study day 84 (week 36) and study day 168 (week 48) office visits.

17.3.4 Physician's Global Assessment (MDGA)

The MDGA evaluates theoverall impact of SSc on the participant as assessed by the physician on a 11-point Numeric rating scale from 0 (excellent) to 10 (extremely poor) (Question - how was your patient's overall health in the last week), with higher scores indicating worse disease in terms of severity, damage, or overall disease.

MDGA will be performed study Day 1, day 84 (week 12) and day 168 (week 24) but will be administered more frequently if clinically indicated. For the extension study, MDGA will be performed at study day 84 (week 36) and study day 168 (week 48) office visits.

To address intra-reader variability in MDGA and to increase interpretability of efficacy measures, MDGA will be performed by the same qualified individual duringthe study, to the extent possible.

17.3.5 Modified Rodnan Skin Score (MRSS):

MRSS is clinician's assessment of skin thickness at 17 prespecified sites on the body with the thickness at each site scored from 0 (uninvolved) to 3 (severe thickening).

The MRSS will be performed during screening (see 8.2.1 Study Population Exclusion Criteria), study day 1, day 84 (week 12) and day 168 (week 24). For the extension study, the MRSS will be performed at study day 84 (week 36) and study day 168 (week 48) office visits.

To address intra-reader variability, mRSS will be performed by the same qualified individual during the study, to the extent possible.

17.3.6 ACR CRISS (American College of Rheumatology Composite Response Index for clinical trials in early diffuse cutaneous Systemic Sclerosis) [150]

ACR CRISS incorporates multisystem involvement in diffuse cutaneous systemic sclerosis and includes the patient's perspective and the impact of the disease on functional disability.

The ACR CRISS is calculated as a 2-step process. The first step evaluates clinically significant decline in renal or cardiopulmonary involvement that is related to SSc and requires treatment. Subjects are considered to be not improved by their treatment if they develop

any one of these four outcomes following treatment, if it appears linked to the disease process:

- New scleroderma renal crisis.
- Decline in FVC % predicted ≥ 15% (relative) confirmed by another FVC % predicted within a month; and if so, a HRCT chest scan to confirm progression ILD.
- A new decline of left ventricular ejection fraction to 45% or less attributable to scleroderma and requiring treatment.
- New onset of pulmonary arterial hypertension attributable to SSc that requires treatment (pulmonary arterial hypertension is defined as mean pulmonary artery pressure ≥ 25 mmHg at rest, an end-expiratory pulmonary wedge pressure ≤ 15 mmHg, and a pulmonary vascular resistance > 3 Wood units).

If any one of these is present, the participant is classified as not improved regardless of changes in other parameters.

The second step assesses participants and calculates the predicted probability of improvement based on changes in the mRSS, FVC % predicted, patient global assessment, physician global assessment, and HAQ-DI.

ACR CRISS will be applied study Day 1 (using FVC % predicted at screening within 21 days), study day 84 (week 12) and study day 168 (week 24). For the extension study ACR CRISS will be applied study day 84 (week 36) and study day 168 (week 48).

17.3.7 Additional clinical efficacy measures

Additional clinical efficacy measures will include:

- Each of the five individual components of ACR CRISS: mRSS (modified Rodnan skin score), FVC % predicted, HAQ-DI (Health Assessment Questionnaire-Disability Index), PtGA (Patient Global Assessment), MDGA (Physician Global Assessment)
- DLCO % predicted
- HRCT chest scan ILD severity using the Goh scoring method [6].
- Additional patient reported outcome Mahler Baseline/Transitional Dyspnea Index (Mahler BDI/TDI).

The additional clinical efficacy measures will be applied study day 1 (using FVC % predicted and DLC0 % predicted at screening visit within 21 days), day 84 (week 12) and day 168 (week 24) except for HRCT chest which will be done at screening and day 168 (week 24). For the extension study the additional clinical efficacy measures will be applied study day 84 (week 36) and day 168 (week 48) except for HRCT chest which will be done only study day 168 (week 48).

Study Measures for the Exploratory Objective Assessing the Effects of Ixazomib onboth Adaptive and Innate Immunopathogenesis of Scleroderma

17.4.1 Blood samples

17.4.1.1 Clinical Immunology Lab Assessments.

In addition to serum protein immunoelectrophoresis, quantitative immunoglobulins (IgG, IgA, IgM), and IgG tetanus toxoid titer included in 17.2.3 Study Measures for the Primary

Objective to Assess the Safety and Tolerability of Ixazomib, additional clinical laboratory immunology testing includes serum antinuclear antibody (ANA) titer; antibody titers to extractable nuclear antigens ENA (inclusive of Scl-70), centromere antibody, and RNA polymerase III; and rheumatoid factor titer for Exploratory Objectives.

Blood samples will be collected at screening visit, study day 1, day 28 (week 4), day 56 (week 8), day 84 (week 12), day 112 (week 16), day 140 (week 20), day 168 (week 24), and at the concluding follow-up study day 196-203 (week 28-29) for participants not proceeding on to the extension study. For the extension study, blood samples will be collected at study day 84 (week 36), day 168 (week 48), and at the concluding follow-up study day 196-203 (week 52-53) office visits..

17.4.1.2 Immunology Research Lab Tests

Blood samples will be obtained to further characterize known markers, explore novel markers of SSc-ILD [153-155], explore other pathways and markers, assess changes in these markers before and after initiation of ixazomib treatment, and further elucidate disease pathobiology and the effects of ixazomib.

Blood (maximum of 40 ml blood in 4 ACD tubes for flow cytometric analysis and serum preparation, one PaxGene tube for RNA and one acid-citrate-dextrose tube for DNA) will be collected at screening visit and study day 1 as baseline samples. Blood samples will also be collected at study day 28 (week 4), day 56 (week 8), day 84 (week 12), day 112 (week 16), day 140 (week 20), day 168 (week 24), and at the concluding follow-up study day 196-203 (week 28-29) office visits for participants not proceeding on to the extension study. For the extension study, blood samples will be collected at study day 84 (week 36), day 168 (week 48), and at the concluding follow-up study day 196-203 (week 52-53) office visits.

Whole blood will be stained for the assessment of immune cell phenotypes of subsets of DCs (pDCs, CD1c+ mDCs, CD141+ mDCs), B cells (naïve, memory, plasmablasts, plasma cells, marginal zone (MZ)-like, subsets of transitional B cells, B10-like, B1), CD4+ T cells (naïve, memory, TH1, TH2, TFH, and Tregs), CD8+ T cells (naïve and memory), NK and NKT cells, innate lymphoid cells (ILCs; ILC1, ILC2, ILC3) [156], and granulocytes (neutrophils, basophils, and eosinophils). The frequency of individual subsets of circulating immune cells as well as their activation status will be assessed.

Whole blood transcriptomics will be assessed by RNA-seq and/or Nanostring assay with selected genes. Planned analyses include IFN and B cell signatures (including BLIMP-1 and plasma cell signatures [116] as well as other potential biomarkers of scleroderma [153, 154], including TGF-beta, connective tissue growth factor, IL-6, CCL2, CXCL4, SP-D, CCL18, IFN-inducible chemokines (CXCL10 and CXCL11), adhesion molecules (ICAM-1, P-selectin, VCAM-1, and E-selectin), vascular biomarkers (including VEGF, endothelin-1, thrombomodulin, BNP, endostatin, and plasminogen), and VEGF [153].

Peripheral blood mononuclear cells (PBMCs) will be isolated by gradient centrifugation and used for further charactering immune cell phenotypes. CD4+ T cell cytokine expression (IFNγ for TH1, IL-4/IL-5/IL-13 expression for TH2, FOXP3/CD25/IL-10/CTLA-4 expression for Tregs,

IL-21 expression for TH21, and IL-17 expression for TH17) and CD8+ T cell functions (Granzyme and cytokine expression), B cell expression of CD80, CD86, CD95, IL-6, IL-10, IL-6R, IL-21R, and TGF-beta), monocyte (CD14+CD16-, CD14+CD16hi, CD14-CD16hi) expression of IL-10, TGF-beta and IL-10 will be assessed by intracellular staining and flow cytometry. The amount of cytokines and chemokines expressed by specific cell types or by total PBMCs can also be assessed by bead-based multiplex assays.

Sera will be prepared and used for assessing serum scleroderma biomarkers. Planned analyses include cartilage oligomeric matrix protein (COMP); activity biomarkers CCL2 (MCP-1), BAFF, APRIL, and adiponectin; severity markers TGF-beta, IL-6 levels, IFN-inducible chemokine score (CXCL10 and CXCL11); predictive markers CXCL4 and CCL18; and semaphorin 3E, measurable circulating proteasomes and *Siglec-1* IFN expression.

17.4.2 Skin Biopsies

Samples collected in this study will be used to further understand the potential impact of ixazomib on SSc. Two standard paired 5 mm forearm skin punch biopsies will be obtained on study day 1, day 84 (week 12) and day 168 (week 24). For the extension study, two standard paired 5 mm forearm skin punch biopsies will be obtained on study day 168 (week 48).

Histology will be performed to characterize the pathology outlines of scleroderma.

Immunohistochemistry will be performed to examine immune cell infiltration. Planned analyses include subsets of DCs (especially pDCs), macrophages (especially M2 macrophages; CD163+CD204+) [66, 89, 157], B cells, and ILCs (especially ILC2). Cytokine expression including IFN-α, IL-6, and TGF-beta) will also be assessed.

Transcriptomics of skin biopsies will be assessed by performing RNA-seq experiments in the Genomics Core in Mayo Clinic. Planned analyses include type 1 IFN and plasma cell gene signatures as well as collagen genes COL1A1, COL3A1, and COL5A1; CCL2, IL-6, CCL18, POSTIN, ENPP2, α-smooth muscle actin, COMP, pSTAT3; and semaphorin 3E. CCL3, IL-7, IL-13, and IFNγ transcripts have been also increased in skin biopsies of scleroderma [158].

Tandem Mass Tag Proteomic analysis of skin biopsies will be performed at the Proteomics Core in Mayo Clinic. Planned analyses include quantitative measurement of >6,000 proteins expressed in skin biopsies collected before and after ixazomib treatment.

18.0 STUDY ASSESSMENTS BY VISIT

The results of all assessments and procedures listed below will be documented in the patient's medical record and recorded in the study records. To the extent possible, a patient's visits will be scheduled at the same time of day.

18.1 Washout Period (≤ 90 days)

A Washout Period will be required for the following patients:

- **Patients not on background SSc-ILD medication at study Day 1:**

  Washout will be required for those patients on an SSc-ILD medication other than MMF (See 8.2.4 Eligibility Criteria Medication Exclusions); those on an excluded

medication (See 8.2.4 Eligibility Criteria Medication Exclusions); and those who smoked tobacco in the 3 months before screening.

- **Patients on background stable oral dose of MMF at study Day 1:**
  Washout will be required for patients on an excluded medication (See 8.2.4 Eligibility Criteria Medication Exclusions) and those who smoked tobacco in the 3 month (90days) before screening.

For those patients requiring medication washout, written informed consent will be obtained and a complete medical history will be taken (including systems review and prior and concomitant medications). The duration of washout will be 28 days for an investigational drug, 3 months (90 days) for tobacco smoking, and at least 5-half-lives for other medications. The number of study candidates needing to wash out medications other than MMF is anticipated to be very low based on the low prevalence of medicines other than MMF used clinically for the treatment of scleroderma-ILD. No study candidate already taking MMF will be asked to wash out MMF.

An HRCT chest scan will be used at screening to confirm eligibility. During the medication washout period, a request will be made to review a participant's previous HRCT chest scan. A HRCT chest scan may be used for this purpose if previously completed within 3 months prior to the date of written informed consent at either washout or screening, as applicable. The HRCT must demonstrate features consistent with SSc-ILD as confirmed following review of the HRCT images by Mayo radiology study staff. If the previous HRCT chest study is determined to be technically inadequate or cannot be made available for review by Mayo radiology study staff, or if the HRCT chest scan was performed more than 3 months prior to signing of written informed consent, a HRCT chest scan will be obtained during study screening.

During the medication washout, study procedures that will be performed during screening at the end of washout will be scheduled.

Participants unable to wash out other SSc-ILD medications and any excluded medications within the specified time frames will be considered ineligible to continue in the study.

18.2 Screening Period (Days -21 to-1)

During screening, which can last ≤ 21 days, the following assessments and procedures will be performed:

1. For patients who do not require medication washout, written informed consent will be obtained before any assessments or procedures are performed.
2. Medical history, as follows:
   a. **For patients who do not require medication washout:** complete medical history including systems review and prior and concomitantmedications
   b. **For patients who require medication washout:** directed medical history including a review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
   c. An inventory of baseline symptoms, including those associated with background therapy if using MMF
3. Physical examination, including vital signs (blood pressure, heart rate, and

respiratory rate), body weight (in kilograms), and height (in centimeters)
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Hematology and serum chemistry blood samples
7. Clinical Immunology Tests blood sample
8. Serum pregnancy test (women of childbearing potential)
9. Blood sample for biomarker analyses
10. 12-lead ECG
11. Complete pulmonary function tests including lung volumes and DLC0 % predicted
12. HRCT chest scan.

    A HRCT chest scan will be used at screening to confirm eligibility. A HRCT chest scan may be used for this purpose if previously completed within 3 months prior to the date of written informed consent at either medication washout or screening, as applicable. The HRCT must demonstrate features consistent with SSc-ILD as confirmed following review of the HRCT images by Mayo radiology study staff. If the previous HRCT chest study is determined to be technically inadequate or cannot be made available for review by Mayo radiology study staff, or if the HRCT chest scan was performed more than 3 months prior to signing of written informed consent, a HRCT chest scan will be obtained during study screening.
13. Resting transthoracic echocardiogram only if not done within 6 months prior to written informed consent.

18.3 Treatment Period (Study Days 1-168)

18.3.1 Study Day 1

If the participant is confirmed to be eligible based on screening the following procedures will be performed on study Day 1:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate), body weight (in kilograms).
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler BDI
    b. SHAQ
    c. PtGA
7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample
10. Serum pregnancy test (women of childbearing potential)
11. Blood sample for biomarker analyses

12. Obtain skin biopsies
13. Dispense ixazomib 4 mg capsules for the 4-week cycle number 1 (3 capsules)
14. The first dose of ixazomib for cycle 1 will be taken on study Day 1 during the study visit and observed being taken by a member of the study team.
15. Instruct the participant on taking ixazomib day 8 and day 15 of the first cycle

18.3.2 Study Day 14 (Week 2) Lab Visit (+4 days)

1. Hematology and serum chemistries blood samples
2. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (Section 9.2 Ixazomib Dose Modification or Interruption); if so, patient is to be contacted by phone to:
    A. Discontinue taking any remaining ixazomib.
    B. Arrange for additional study office visit (Unscheduled Study Visit, Section 19.0) prior to anticipated ixazomib dosing on day 15, if applicable.
    C. Initiate additional test monitoring per Sections 9.2.2 Hematologic Toxicity and 9.2.3.3 Hepatic Impairment as applicable.
3. At add-on study office visit:
    A. If applicable, collect unused ixazomib intended for use day 15.
    B. Implement designated ixazomib dose modification / interruption and monitoring of clinical laboratory assessments specified in Sections 9.2.2 and 9.2.3.3 as applicable.
    C. If applicable and on ixazomib cycle day 15 only, dispense a single revised ixazomib dose and observe being taken by a member of the study team.

18.3.3 Study Day 28 (Week 4) Office Visit (± 4days)

On study day 28 the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. UCLA SCTC GIT 2.0 questionnaire
4. Hematology and serum chemistries blood samples
5. Clinical Immunology Tests blood sample
6. Serum pregnancy test (women of childbearing potential)
7. Blood sample for biomarker analyses
8. Spirometry and DLCO
9. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.
10. Collect unused ixazomib
11. Dispense ixazomib dosing indicated for the 4-week cycle number 2 (3 capsules)
12. If not interrupted, the first dose of ixazomib (day 1) for the cycle 2 will be taken during the study day 28 visit and observed being taken by a member of the study

team.

13. Instruct the participant on taking ixazomib day 8 and day 15 of the second cycle.

18.3.4 Study Day 42 (Week 6) Lab Visit (+4 days)

1. Hematology and serum chemistries blood samples
2. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (Section 9.2 Ixazomib Dose Modification or Interruption); if so, patient is to be contacted by phone to:
    A. Discontinue taking any remaining ixazomib.
    B. Arrange for additional study office visit (Unscheduled Study Visit, Section 19.0) prior to anticipated ixazomib dosing on day 15, if applicable.
    C. Initiate additional test monitoring per Sections 9.2.2 Hematologic Toxicity and 9.2.3.3 Hepatic Impairment as applicable.
3. At add-on study office visit:
    A. If applicable, collect unused ixazomib intended for use day 15.
    B. Implement designated ixazomib dose modification / interruption and monitoring of clinical laboratory assessments specified in Sections 9.2.2 and 9.2.3.3 as applicable.
    C. If applicable and on ixazomib cycle day 15 only, dispense a single revised ixazomib dose and observe being taken by a member of the study team.

18.3.5 Study Day 56 (Week 8) Office Visit (± 4 days)

On study day 56 the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. UCLA SCTC GIT 2.0 questionnaire
4. Hematology and serum chemistries blood samples
5. Clinical Immunology Tests blood sample
6. Serum pregnancy test (women of childbearing potential)
7. Blood sample for biomarker analyses
8. Spirometry and DLCO
9. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.
10. Collect unused ixazomib
11. Dispense ixazomib dosing indicated for the 4-week cycle number 3 (3 capsules)
12. If not interrupted, the first dose of ixazomib (day 1) for the cycle 3 will be taken during the study day 56 visit and observed being taken by a member of the study team.
13. Instruct the participant on taking ixazomib day 8 and day 15 of the third cycle.

18.3.6 Study Day 70 (Week 10) Lab Visit (+4 days)

1. Hematology and serum chemistries blood samples
2. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (Section 9.2 Ixazomib Dose Modification or Interruption); if so, patient is to be contacted by phone to:
    A. Discontinue taking any remaining ixazomib.
    B. Arrange for additional study office visit (Unscheduled Study Visit, Section 19.0) prior to anticipated ixazomib dosing on day 15, if applicable.
    C. Initiate additional test monitoring per Sections 9.2.2 Hematologic Toxicity and 9.2.3.3 Hepatic Impairment as applicable.
3. At add-on study office visit:
    A. If applicable, collect unused ixazomib intended for use day 15.
    B. Implement designated ixazomib dose modification / interruption and monitoring of clinical laboratory assessments specified in Sections 9.2.2 and 9.2.3.3 as applicable.
    C. If applicable and on ixazomib cycle day 15 only, dispense a single revised ixazomib dose and observe being taken by a member of the study team.

18.3.7 Study Day 84 (Week 12) Office Visit (± 4 days)

On study day 84 the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, andrespiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PtGA
7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample
10. Serum pregnancy test (women of childbearing potential)
11. Blood sample for biomarker analyses
12. Complete pulmonary function tests including lung volumes and DLC0 % predicted
13. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next

treatment cycle.

14. Collect unused ixazomib
15. Dispense ixazomib dosing indicated for the 4-week cycle number 4 (3 capsules)
16. If not interrupted, the first dose of ixazomib (day 1) for the cycle 4 will be taken during the study day 84 visit and observed being taken by a member of the study team.
17. Instruct the participant on taking ixazomib day 8 and day 15 of the fourthcycle.

18.3.8 Study Day 112 (Week 16) Office Visit (± 4days)

On study day 112 the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. UCLA SCTC GIT 2.0 questionnaire
4. Hematology and serum chemistries blood samples
5. Clinical Immunology Tests blood sample
6. Serum pregnancy test (women of childbearing potential)
7. Blood sample for biomarker analyses
8. Spirometry and DLCO
9. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.
10. Collect unused ixazomib
11. Dispense ixazomib dosing indicated for the 4-week cycle number 5 (3 capsules)
12. If not interrupted, the first dose of ixazomib (day 1) for the cycle 5 will be taken during the study day 112 visit and observed being taken by a member of the study team.
13. Instruct the participant on taking ixazomib day 8 and day 15 of the fifth cycle.

18.3.9 Study Day 140 (Week 20) Office Visit (± 4 days)

On study day 140 the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. UCLA SCTC GIT 2.0 questionnaire
4. Hematology and serum chemistries blood samples
5. Clinical Immunology Tests blood sample
6. Serum pregnancy test (women of childbearing potential)
7. Blood sample for biomarker analyses
8. Spirometry and DLCO
9. Determine if ixazomib dose modification/interruption for hematologic or non-

hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.

10. Collect unused ixazomib
11. Dispense ixazomib dosing indicated for the 4-week cycle number 6 (3 capsules)
12. If not interrupted, the first dose of ixazomib (day 1) for the cycle 6 will be taken during the study day 140 visit and observed being taken by a member of the study team.
13. Instruct the participant on taking ixazomib day 8 and day 15 of the sixth cycle.

18.3.10 Study Day 168 (Week 24) Office Visit (± 4 days)

On study day 168 the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and repository rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PTGA
7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample
10. Serum pregnancy test (women of childbearing potential)
11. Blood sample for biomarker analyses
12. Complete pulmonary function tests including lung volumes and DLC0 % predicted
13. HRCT chest scan
14. Obtain skin biopsies
15. Collect unused ixazomib

18.3.11 Study Post-Treatment Follow-up Day 196-203 (Week 28-29) Office Visit (28–35 days after last study visit day 168/week 24)

On study day 196-203 post-treatment follow-up visit, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. Hematology and serum chemistries blood samples
5. Clinical Immunology Tests blood sample

6. Serum pregnancy test (women of childbearing potential)
7. Blood sample for biomarker analyses

19.0 UNSCHEDULED VISITS

The minimum acceptable frequency of participant visits and the monitoring clinical laboratory values is specified in Section 18.0 Study Assessments by Visit and Schedule of Study Evaluations and Procedures: Washout Through Follow-Up (Appendix A). Additional visits and/or clinical laboratory tests to monitor toxicity will be performed as indicated and their frequency will depend on concurrent medical condition(s) and concomitant medication use.

20.0 PATIENTS LOST TO FOLLOW-UP

If a participant misses a visit and is not responding to telephone calls (all attempts to contact the patient will be documented), more concerted action in locating the patient will be taken. At least two attempts will be made to contact the patient by telephone and two additional attempts to contact the patient's emergency contact if this information is available. If these attempts are not successful, then a registered letter will be sent to the last known address of the participant. If this is unsuccessful, then the participant will be considered lost to follow-up and discontinued from the study.

21.0 ADVERSE EVENTS

21.1 Definitions

21.1.1 Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms will be recorded.

Adverse events include:

- A clinical event occurring from the time a participant provides written informed consent and before ixazomib is initiated on study day 1.
- Onset of a clinical event after ixazomib is initiated on study day 1.
- An increase in the frequency, severity, and/or seriousness of a preexisting condition during the study, including scleroderma.
- Worsening of preexisting condition leading to over overnight hospitalization will be reported as a serious adverse event (SAE).

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms will be identified and recorded. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome, it will be recorded as a separate adverse event.

Adverse events will not include:

- Events identified at screening visit that meet exclusioncriteria
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); a condition leading to the medical or surgical procedure will be recorded as the adverse event, not the procedure itself.
- Situations where an untoward medical occurrence has not taken place. Examples may include:
    - Hospitalizations planned for a pre-existing condition which has notworsened
    - Hospitalizations that occur for treatment procedures not due to an AE or SAE.
    - Hospitalizations for a diagnostic procedure where the hospitalization does not routinely require overnight stay.
    - Overdose or misuse of ixazomib or any concomitant therapy that does not result in any adverse signs or symptoms

For laboratory safety measurements, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered as clinically significant will be recorded as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory measurements can be recorded as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory abnormalities or other abnormal clinical findings will be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality
- If action with study drug ixazomib is taken to reduce or interrupt it's dosing as a result of the abnormality
- Based on the clinical judgment of the Investigator

Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

Laboratory results will not be reported as AEs in the following cases:

- Laboratory measurements already outside the reference range at screening, unless a further increase / decrease is considered an exacerbation of a pre-existing condition.
- Abnormal laboratory results caused by mechanical or physical influences on the blood sample (e.g., in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- An abnormal laboratory value that cannot be confirmed after repeat analysis (i.e., the previous result could be marked as not valid and will not necessarily be reported as an AE).

21.1.2 Serious Adverse Event (SAE)

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

- Death.

The SAE event must be the cause of death to meet this criterion.

- A life-threatening adverse event.
  An adverse event is considered "life-threatening" if, in the view of the investigator its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires in-hospitalization or prolongation of existing hospitalization.
  Any hospital admission with at least 1 overnight stay will be considered an in-patient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery or procedure will be recorded as adverse events and assessed for seriousness. Worsening of a pre-existing condition leading to hospitalization will be reported as an SAE. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered an inpatient hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.
  Important medical events that do not meet any of the above criteria may be an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

21.2 Assessment of Adverse Events

The severity (intensity) of each adverse event will be assessed as mild, moderate, or severe, and each adverse event will be categorized as to its potential relationship to the study drug ixazomib using the categories of yes or no.

21.2.1 Severity Assessment

The severity of each AE (i.e., nonserious and serious) will be assessed as follows:

- **Mild severity:** A type of AE that is usually transient, easily tolerated, causing minimal discomfort not generally interfering with usual activities of daily living, and may require only minimal treatment or therapeutic intervention.
- **Moderate severity:** A type of AE that is sufficiently discomforting so as to interfere with usual activities of daily living and is usually alleviated with additional specific therapeutic intervention.
- **Severe severity:** A type of AE that is incapacitating with inability to work or perform usual activities of daily living, or significantly affects clinical status, and may require intensive therapeutic intervention.

21.2.2 Causality Assessment

The relationship of an adverse event to the administration of the study drug ixazomib will be assessed according to the following definitions:

- **No** (unrelated, not related, unlikely to be related) – The time course between the administration of ixazomib and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications) is suspected.
- **Yes** (possibly, probably, or definitely related) – The time course between the administration of ixazomib and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug ixazomib. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors will also be considered in assessing causality:

- Temporal sequence from ixazomib administration:
  The adverse event should occur after the study drug ixazomib was initiated on study day 1. The length of time from ixazomib exposure to the event will be evaluated in the clinical context of the event. Treatment-emergent adverse events will be captured in relation to the ixazomib dose, the need for dose reduction or interruption, and any recurrence of the AE upon re-initiation of ixazomib as permitted per the protocol.
- Preexisting and concomitant illnesses:
  Each AE and SAE will be evaluated in the context of the natural history and course of the scleroderma being treated and any other illness, pre-existing or new, the participant is experiencing.
- Concomitant drugs:
  Other drugs the participant is taking or the treatment the participant receives will be evaluated to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug:
  Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

21.3 Observation Period for Adverse Events

The period of observation for AEs and SAEs for each participant will extend from the time of the participant providing written informed consent until completion of the post-treatment follow-up visit scheduled to occur 28-35 days after the last study visit on day 168/week 24. Participants will be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study treatment.

21.4 Follow-Up of Adverse Events

Every effort will be made to follow AEs until resolution or stabilization. Ongoing, unrelated, nonserious AEs that have not resolved or stabilized and are not clinically significant will be followed until the participant completes the study. Serious adverse events will be followed until the SAE resolves, stabilizes, the participant is lost to follow-up, or death.

22.0 PREGNANCY

A pregnancy occurring during the study is not considered an AE or SAE**.** In the event of pregnancy, the participant will immediately discontinue the study drug ixazomib and will be discontinued from the study following early completion of the post-treatment follow-up visit scheduled day 196-203 (week 28-29) and in the extension study day 196-203 (week 48).

23.0 REPORTING TO TAKEDA

23.1 Adverse Events

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

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

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

Since this is an investigator-initiated study, the principal investigator, Leroy Griffing, MD, 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 IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to Takeda Pharmacovigilance (or designee):

- Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event
- All other serious (non-fatal/non-life-threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

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

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

The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 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 Takeda.

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 Takeda 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 Takeda 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 Takeda 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

[redacted]

Suggested Reporting Form:

- SAE Report Form (provided by Takeda)
- US FDA MedWatch 3500A:

  [redacted]
- Any other form deemed appropriate by the sponsor-investigator

23.2 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 Takeda

and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate CRF form. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints or Medication Errors (Including Overdose)

- [redacted]

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 Takeda Pharmacovigilance.

23.3 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study or within 90 days after the last dose, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must immediately fax a completed Pregnancy Form to the Takeda Department of Pharmacovigilance or designee. 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 Takeda 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 Takeda)

24.0 STATISTICAL METHODS and ANALYSES

24.1 Analysis Population

The primary analysis population will be:

- **Safety Population:** All patients who provide written informed consent, and receive at least one dose of ixazomib

24.2 Hypothesis Testing

No formal hypothesis testing will be done.

24.3 Demographics and Baseline Disease Characteristics

The safety population will be used for the analysis of demographic and baseline disease characteristics data. Descriptive statistics will be used to summarize demographic and baseline patient characteristics. Continuous-scaled variables (e.g., age) will be summarized

with the number of observations (N), mean, standard deviation, median, quartile, and minimum and maximum. Categorical variables (e.g., sex) will be summarized using patient counts and percentages. Baseline medical histories and pre-existing conditions will be summarized based on mapping to system organ classes and preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA). Prior medications will be summarized by titration group, based on mapping to drug classes and generic terms in the World Health Organization (WHO) Drug Dictionary.

24.4 Dosing and Duration of Exposure

The safety population will be used for the analysis of study drug dosing and duration of exposure. The total duration of exposure will be defined as the time interval between the first dose and the last dose of ixazomib (inclusive), based on the patient study drug dosing information. Total duration of exposure to study drug (in weeks) will be summarized by descriptive statistics (i.e., N, mean, standard deviation, median, quartile, and minimum and maximum).

The number and percentage of patients requiring dose reductions, modifications, and discontinuations will be summarized by group.

24.5 Safety Analyses

The safety population will be used for the analysis of safety data. Summaries of AEs, deaths, and patient disposition will be presented, comparing patients in the two treatment groups. Study periods will be comprised of the following:

- Entire 24-week study period
- First 12 weeks of treatment
- Subsequent 12 weeks of treatment

Safety measurements will include the following:

- Treatment-emergent AEs
- Treatment-emergent SAEs
- Treatment-emergent treatment-related AEs
- Treatment-emergent treatment-related SAEs
- Treatment-emergent AEs leading to ixazomib dose modifications
- Treatment-emergent AEs leading to early discontinuation of ixazomib
- Treatment-emergent changes in clinical laboratory measures
- Treatment emergent changes in patient vital signs
- Treatment emergent changes in UCLA SCTC GIT 2.0 questionnaire

AEs will be mapped to system organ classes and preferred terms in MedDRA. Treatment emergent events are defined as those that start or worsen after the start of study treatment through 28 days after the last dose of study treatment. AEs will be summarized by treatment group, system organ class, and preferred term, and by event severity and the event's relationship to study treatment. At each level of summation, patients will be counted only once, under the greatest severity and strongest study-drug relationship.

Clinical laboratory data will be summarized at each measurement time point and for each patient's final post-baseline measurement in the following ways:

(1) with descriptive statistics (mean, standard deviation, median, and range) for each

measurement time point;
(2) with descriptive statistics for the change from baseline in the measurements at each post-baseline time point; and
(3) with tables summarizing the frequencies of patients below, within, and above the normal ranges at each time point as compared with baseline. All clinical laboratory values collected during the study will be listed, with values outside the normal ranges flagged for clinical evaluation. Grade 3 and 4 laboratory results will be listed and summarized.

Vital signs will be summarized by group and listed by patient.

Data from the UCLA SCTC GIT 2.0 questionnaire at each assessment time will be summarized descriptively without imputation for missing values.

Concomitant medications will be summarized by treatment group based on mapping to drugclasses and generic terms in the WHO Drug Dictionary.

24.6 Clinical Efficacy Analysis

24.6.1 ACR CRISS (American College of Rheumatology Composite Response Index for clinical trials in early diffuse cutaneous Systemic Sclerosis)

ACR CRISS incorporates multisystem involvement in diffuse cutaneous systemic sclerosis/scleroderma and includes the patient's perspective and the impact of the disease on functional disability (17.3.6 Description of Study Measures, ACR CRISS).

The ACR CRISS is calculated as a 2-step process. The four individual possible outcomes of Step 1 ACR CRISS which include new scleroderma renal crisis, decline in % predicted ≥ 15% (relative), new decline of left ventricular ejection fraction to 45% or less attributable to scleroderma, and new onset pulmonary arterial hypertension attributable to scleroderma will be tabulated and summarized descriptively for both treatment groups at study Day 1, study day 84 (week 12) and study day 168 (week 24).

Step 2 ACR CRISS calculates changes from baseline in the predicted probability of improvement and will be applied and summarized descriptively for both treatment groups at study day 84 (week 12) and study day 168 (week 24).

24.6.2 Additional Assessments for Clinical Efficacy

Analysis of these additional efficacy assessments will be based on the safety population. Clinical efficacy assessments will include each of the individual components of ACR CRISS as follows:

- mRSS (modified Rodnan skin score)
- FVC % predicted
- HAQ-DI (Health Assessment Questionnaire-Disability Index)
- PtGA (Patient Global
- MDGA (Physician Global Assessment)

Additional clinical efficacy measures include:

- DLCO % predicted
- HRCT chest scan ILD severity using the Goh scoring method
- Patient reported outcome Mahler Baseline/Transitional Dyspnea Index (Mahler BDI/TDI).

The results of mRSS score and changes from baseline at study day 84 (week 12) and study day 168 (week 24) will be summarized without imputation for missing values.

The percent predicted FVC and DLCO results and change from screening at study day 28 (week 4), day 56 (week 8), day 84 (week 12), day 112 (week 16), day 140 (week 20) and study day 168 (week 24) will be summarized descriptively without imputation for missing values. Total lung capacity results and change from screening at study day 84 (week 12) and study day 168 (week 24) will be summarized descriptively without imputation for missing values.

HRCT chest scan Goh scoring of ILD severity and change from baseline at study day 168 (week 24) will be summarized descriptively.

The results for each of the disease-status scales Mahler BDI/TDI, SHAQ, PtGA and MDGA and changes from baseline at study day 84 (week 12) and study day 168 (week 24) will be summarized descriptively without imputation for missing values.

24.7 Post-Discontinuation Assessments for Safety

Participants who prematurely and permanently discontinue ixazomib study medication and continue with post-discontinuation monitoring visits will be used for the analysis of post-discontinuation safety data. Summaries of AEs, deaths, and patient disposition will be presented.

Safety outcome measures used will include, but will not be limited to:

- Treatment-emergent (not ixazomib) AEs
- Treatment-emergent (not ixazomib) SAEs
- Treatment-emergent (not ixazomib) treatment-related AEs
- Treatment-emergent (not ixazomib) treatment-related SAEs
- Treatment-emergent (not ixazomib) changes in clinical laboratory measures
- Treatment emergent (not ixazomib) changes in patient vital signs
- Treatment emergent (not ixazomib) changes in UCLA SCTC GIT 2.0 questionnaire

24.8 Post-Discontinuation Clinical Efficacy Analysis

Participants who prematurely and permanently discontinue ixazomib study medication and continue monitoring with post-discontinuation visits will be used for the analysis of post-discontinuation clinical efficacy data.

24.8.1 Post-Discontinuation ACR CRISS (American College of Rheumatology Composite Response Index for clinical trials in early diffuse cutaneous Systemic Sclerosis)

ACR CRISS incorporates multisystem involvement in diffuse cutaneous systemic

sclerosis/scleroderma and includes the patient's perspective and the impact of the disease on functional disability (17.3.6 Description of Study Measures, ACR CRISS).

The ACR CRISS is calculated as a 2-step process. The four individual possible outcomes of Step 1 ACR CRISS which include new scleroderma renal crisis, decline in FVC % predicted ≥ 15% (relative), new decline of left ventricular ejection fraction to 45% or less attributable to scleroderma, and new onset pulmonary arterial hypertension attributable to scleroderma will be tabulated and summarized descriptively for post-discontinuation visit 3 (PD day 84 ± 4 days) as required and the final post-discontinuation visit.

Step 2 ACR CRISS calculates changes from baseline in the predicted probability of improvement and will be applied and summarized descriptively for post-discontinuation visit 3 (PD day 84 ± 4 days) as required and the final post-discontinuation visit.

24.8.2 Additional Assessments for Post-Discontinuation Clinical Efficacy

Clinical efficacy assessments will include each of the individual components of ACR CRISS as follows:

- mRSS (modified Rodnan skin score)
- FVC % predicted
- HAQ-DI (Health Assessment Questionnaire-Disability Index)
- PtGA (Patient Global
- MDGA (Physician Global Assessment)

Additional clinical efficacy measures include:

- DLCO % predicted
- Patient reported outcome Mahler Baseline/Transitional Dyspnea Index (Mahler BDI/TDI).

The results of mRSS score and change from the date of completion of the early discontinuation assessments and procedures as planned for study day 168 (week 24), post-discontinuation visit 3 (PD day 84) as necessary and the final post-discontinuation visit will be summarized without imputation for missing values.

The percent predicted FVC and DLCO results and change from the date of completion of the early discontinuation assessments and procedures as planned for study day 168 (week 24), post-discontinuation visit 3 (PD day 84) as necessary and the final post-discontinuation visit will be summarized descriptively without imputation for missing values. Total lung capacity results and change from the date of completion of the early discontinuation assessments and procedures as planned for study day 168 (week 24), post-discontinuation visit 3 (PD day 84) as necessary and the final post-discontinuation visit will be summarized descriptively without imputation for missing values.

The results for each of the disease-status scales Mahler BDI/TDI, SHAQ, PtGA and MDGA and changes from the date of completion of the early discontinuation assessments and procedures as planned for study day 168 (week 24), post-discontinuation visit 3 (PD day 84 ± 4 days) as necessary and the final post-discontinuation visit will be summarized descriptively without imputation for missing value.

25.0 24-WEEK EXTENSION STUDY

25.1 Eligibility

Only participants continuing to use ixazomib and completing the initial 24-week safety and tolerability study will be eligible to continue their participation in a 24-week extension study. Participants proceeding on to the extension study will not complete the initial study follow-up day 196-203 (week 28-29) office visit (see 18.3.11).

In the 24-week extension study, ixazomib dosing will continue orally on days 1, 8, and 15 of 28-day treatment cycle for 6 cycles. The first dose of ixazomib for each cycle will continue to be taken as part of the extension study office visits assessments and procedures.

25.2 EXTENSION STUDY ASSESSMENTS BY VISIT

25.2.1 Study Day 168 (Week 24) Office Visit (±4 days)

For those participants taking ixazomib and proceeding on to the 24-week extension study, at the last study day 168 (week 24) office visit the same assessments and procedures will be performed (see 18.3.10):

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PtGA
7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample
10. Serum pregnancy test (women of childbearing potential)
11. Blood sample for biomarker analyses
12. Complete pulmonary function tests including lung volumes and DLC0 % predicted
13. HRCT chest scan
14. Obtain skin biopsies
15. Collect unused ixazomib

For those participants proceeding on to the 24-week extension study, at the last study day 168 (week 24) office visit (see 18.3.10) the following additional assessments and procedures will be performed:

16. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with

clinical laboratory assessments more frequently if indicated for the next treatment cycle.

17. Dispense ixazomib dosing indicated to begin cycle 1 (3 capsules) of the extension study.
18. If not interrupted, the first dose of ixazomib (day 1) for cycle 1 of the extension study will be taken during the study day 168 office visit and observed being taken by a member of the study team.
19. Instruct the participant on taking ixazomib day 8 and day 15 of cycle 1 of the extension study.

25.2.2 Extension Study Day 28 (Week 28) Office Visit (±4 days)

On extension study day 28, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. Hematology and serum chemistries blood samples
4. Serum pregnancy test (women of childbearing potential)
5. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.
6. Collect unused ixazomib**.**
7. Dispense ixazomib dosing indicated for cycle 2 (3 capsules) of the extension study.
8. If not interrupted, the first dose of ixazomib (day 1) for cycle 2 of the extension study will be taken at the extension study day 28 office visit and observed being taken by a member of the study team.
9. Instruct the participant on taking ixazomib day 8 and day 15 of cycle 2 of the extension study.

25.2.3 Extension Study Day 56 (Week 32) Office Visit (±4 days)

On extension study day 56, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. Hematology and serum chemistries blood samples
4. Serum pregnancy test (women of childbearing potential)
5. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.
6. Collect unused ixazomib**.**
7. Dispense ixazomib dosing indicated for cycle 3 (3 capsules) of the extension study.
8. If not interrupted, the first dose of ixazomib (day 1) for cycle 3 of the extension study will be taken at the extension study day 56 office visit and observed being taken by a member of the study team.

9. Instruct the participant on taking ixazomib day 8 and day 15 of cycle 3 of the extension study.

25.2.4 Extension Study Day 84 (Week 36) Office Visit (±4 days)

On extension study day 84, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PtGA
7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample
10. Serum pregnancy test (women of childbearing potential)
11. Blood sample for biomarker analyses
12. Complete pulmonary function tests including lung volumes and DLC0 % predicted
13. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.
14. Collect unused ixazomib
15. Dispense ixazomib dosing indicated for cycle 4 (3 capsules) of the extension study.
16. If not interrupted, the first dose of ixazomib (day 1) for cycle 4 of the extension study will be taken at the extension study day 84 office visit and observed being taken by a member of the study team.
17. Instruct the participant on taking ixazomib day 8 and day 15 of cycle 4 of the extension study.

25.2.5 Extension Study Day 112 (Week 40) Office Visit (±4 days)

On extension study day 112, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. Hematology and serum chemistries blood samples
4. Serum pregnancy test (women of childbearing potential)
5. Determine if ixazomib dose modification/interruption for hematologic or non-

hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.

6. Collect unused ixazomib**.**
7. Dispense ixazomib dosing indicated for cycle 5 (3 capsules) of the extension study.
8. If not interrupted, the first dose of ixazomib (day 1) for cycle 5 of the extension study will be taken at the extension study day 112 office visit and observed being taken by a member of the study team.
9. Instruct the participant on taking ixazomib day 8 and day 15 of cycle 5 of the extension study.

25.2.6 Extension Study Day 140 (Week 44) Office Visit (±4 days)

On extension study day 140, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. Hematology and serum chemistries blood samples
4. Serum pregnancy test (women of childbearing potential)
5. Determine if ixazomib dose modification/interruption for hematologic or non-hematologic AE/SAE is indicated (see 9.2 Ixazomib Dose Modification or Interruption); if so, implement designated dose modification/interruption with clinical laboratory assessments more frequently if indicated for the next treatment cycle.
6. Collect unused ixazomib**.**
7. Dispense ixazomib dosing indicated for cycle 6 (3 capsules) of the extension study.
8. If not interrupted, the first dose of ixazomib (day 1) for cycle 6 of the extension study will be taken at the extension study day 140 office visit and observed being taken by a member of the studyteam.
9. Instruct the participant on taking ixazomib day 8 and day 15 of cycle 6 of the extension study.

25.2.7 Extension Study Day 168 (Week 48) Office Visit (±4 days)

On extension study day 168, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitantmedications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. mRSS
5. UCLA SCTC GIT 2.0 questionnaire
6. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PTGA
7. MDGA
8. Hematology and serum chemistries blood samples
9. Clinical Immunology Tests blood sample

10. Serum pregnancy test (women of childbearing potential)
11. Blood sample for biomarker analyses
12. Complete pulmonary function tests including lung volumes and DLC0 % predicted
13. HRCT chest scan
14. Obtain skin biopsies
15. Collect unused ixazomib

25.2.8 Extension Study Day 196-203 (Week 52-53) Follow-up Office Visit (28–35 days after extension study day 168 /week 48 office visit)

On extension study day 196-203, the following assessments and procedures will be performed:

1. Directed medical history including review of AEs/SAEs and concomitantmedications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. Hematology and serum chemistries blood samples
5. Clinical Immunology Tests blood sample
6. Serum pregnancy test (women of childbearing potential)
7. Blood sample for biomarker analyses

25.3 EXTENSION STUDY EARLY DISCONTINUATION

Patients will be free to discontinue their participation in the extension study at any time and without prejudice to further treatment. In addition, patients will permanently discontinue study drug and will be discontinued from the extension study for any of the following reasons:

- Unacceptable toxicity
- Interruption of extension study treatment for >28 days because of an AE(s)
- Patients who were on no background SSc-ILD medication at extension study entry and need to begin a SSc-ILD medication:
    - A decline of FVC by ≥15% predicted or a decline of DLC0 by ≥ 15% predicted observed during the study that is sustained 4 weeks, or a decline of FVC itself to <45% predicted or decline of DLCO itself to <40% predicted observed during the study and if not explained by alternative etiology otherthan worsening scleroderma-related ILD as confirmed by HRCT chest scan will be considered meaningful differences in regards to the participant's background pulmonary status. In such an event, the patient will be discontinued from the study and will proceed to complete early discontinuation assessments and procedures.
- Patients on background MMF at extension study entry who need either (1) to switch to another background SSc-ILD medication, or (2) to begin additional treatment with another background SSc-ILD medication:
    - A decline of FVC by ≥15% predicted or a decline of DLC0 by ≥ 15% predicted observed during the study that is sustained 4 weeks, or a decline of FVC itself to

<45% predicted or decline of DLCO itself to <40% predicted observed during the study and if not explained by alternative etiology otherthan worsening scleroderma-related ILD as confirmed by HRCT chest scan will be considered meaningful differences in regards to the participant's background pulmonary status. In such an event, background MMF may not be switched to another agent in the study nor is the addition of other background medication permitted in the study; if this is necessary, the patient will be discontinued from the study and will proceed to complete early discontinuation assessments and procedures.

- Need for a prohibited medication
- Pregnancy
- Organ, stem cell, or bone marrow transplant
- At the discretion of the investigator

For participants taking no background SSc-ILD medication at extension study entry who need to begin a SSc-ILD medication and participants on background MMF at extension study entry who need either (1) to switch to another background SSc-ILD medication, or (2) to begin additional treatmentwith another background SSc-ILD medication, the new SSc-ILD medication will be prescribed as routine clinical care and will not be provided as part of the study.

25.3.1 EXTENSION STUDY EARLY DISCONTINUATION ASSESSMENTS AND PROCEDURES

Participants who prematurely and permanently discontinue ixazomib extension study treatment will return to the clinic as soon as possible after the last dose of ixazomib and not later than 10 days after that dose to complete early discontinuation assessments and procedures as planned for the last extension study day 168 (week 48) office visit (see 25.2.7).

25.3.2 EXTENSION STUDY EARLY DISCONTINUATION FOLLOW-UP OFFICE VISIT

Participants who prematurely and permanently discontinue ixazomib extension study treatment will again return to the clinic 28-35 days after finishing the early extension study discontinuation assessments and procedures visit (see 25.3.1) to complete the early assessments and procedures as planned for extension study day 196-203 (week 52-53) follow-up office visit (see 25.2.8).

25.3.3 EXTENSION STUDY POST-DISCONTINUATION MONITORING

Participants who prematurely and permanently discontinues ixazomib extension study treatment will be discontinued from the study and will be encouraged to continue post-discontinuation monitoring if eligible to do so.

25.3 EXTENSION STUDY POST-DISCONTINUATION MONITORING FOR SAFETY AND EFFICACY OBJECTIVES

25.4.1 Eligibility for Post-Discontinuation Monitoring for Safety and Efficacy Objectives

Participants who have prematurely and permanently discontinued ixazomib extension study medication for any of the following reasons will be encouraged to continue monitoring for safety and efficacy objectives:

- Unacceptable toxicity

- Interruption of extension study treatment for >28 days because of an AE(s)
- Patients who were on no background SSc-ILD medication at extension study entry and need to begin a SSc-ILD medication
- Patients on background MMF at extension study entry who need either (1) to switch to another background SSc-ILD medication, or (2) to begin additional treatment with another background SSc-ILD medication
- Need for a prohibited medication
- At the discretion of the investigator

25.4.2 Extension Study Post-Discontinuation Monitoring Visits

Based on the date of completion of the early discontinuation assessments and procedures as planned for extension study day 168 (week 48)(Section 25.2.7), eligible participants remaining in the extension study will continue monitoring subsequently every 28 days (± 4 days) for safety and efficacy objectives. Participants initiating extension study post-discontinuation monitoring visits will not complete the extension study early follow-up visit day 196-203 assessments and procedures (see 25.3.2).

25.4.2.1 Extension Study Post-Discontinuation Monitoring (ESPD) Visit 1 (ESPD Day 28 ±4 days), Visit 2 (ESPD Day 56 ±4 days), Visit 4 (ESPD Day 112 ±4 days), and **Visit 5 (ESPD Day 140 ± 4 days) as applicable**

Extension study post-discontinuation monitoring visits ESPD Visit 1, ESPD Visit 2, ESPD Visit 4, and ESPD Visit 5 as applicable will include the following assessments and procedures:

1. Directed medical history including review of AEs/SAEs and concomitantmedications that have been taken since the preceding visit.
2. If participant is taking background MMF, confirm dose and timing of dosing.
3. Name and dose of other SSc-ILD medication if applicable
4. Hematology and serum chemistries blood samples

25.4.2.2 Extension Study Post-Discontinuation Monitoring Visit 3 (ESPD Day 84 ±4 days) and Post-Discontinuation Monitoring Visit 6 (ESPD Day 168 ±4 days) as applicable

Extension study post-discontinuation monitoring visits ESPD Visit 3 day 84 and ESPD Visit 6 day 168 as applicable will include the following assessments and procedures:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. Name and dose of other SSc-ILD medication if applicable
5. mRSS
6. UCLA SCTC GIT 2.0 questionnaire
7. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PtGA
8. MDGA
9. Hematology and serum chemistries blood samples

10. Clinical Immunology Tests blood sample
11. Blood sample for biomarker analyses
12. Complete pulmonary function tests including lung volumes and DLC0 % predicted

25.4.2.3 Extension Study Final Post-Discontinuation Visit

Regardless of the number of extension study post-discontinuation visits needed every 28 days following the date of completion of the early discontinuation assessments and procedures as planned for the last extension study day 168 office visit (week 48)(see 25.2.7), the final extension study post-discontinuation visit will occur at a time point between what would have been extension study day office visit 168 (week 48) and extension study follow-up office visit day 196-203 (week 52-53) if the participant had been still taking study medication. The final post-discontinuation visit will include following assessments and procedures:

1. Directed medical history including review of AEs/SAEs and concomitant medications that have been taken since the preceding visit.
2. Physical examination, including vital signs (blood pressure, heart rate, and respiratory rate) and body weight (in kilograms)
3. If participant is taking background MMF, confirm dose and timing of dosing.
4. Name and dose of other SSc-ILD medication if applicable
5. mRSS
6. UCLA SCTC GIT 2.0 questionnaire
7. Disease-status scales:
    a. Mahler TDI
    b. SHAQ
    c. PtGA
8. MDGA
9. Hematology and serum chemistries blood samples
10. Clinical Immunology Tests blood samples
11. Blood sample for biomarker analyses
12. Complete pulmonary function tests including lung volumes and DLC0 % predicted
13. HRCT chest scan

25.5 EXTENSION STUDY STATISTICAL METHODS and ANALYSES

25.5.1 Extension Study Safety Analyses

The safety population as per Section 24.1 will be used for the analysis of safety data. Summaries of AEs, deaths, and patient disposition will be presented comparing participants in the two treatment groups, those who are taking background MMF and those who are not taking background SSc-ILD medication.

In addition to the initial study treatment periods as described in Safety Analyses Section 24.5 comprised of the first 12 weeks of treatment, the second 12 weeks of treatment, and the entire 24 weeks of the initial study, additional extension study treatment periods will be included in the safety analyses comprised of:

- the first 12 weeks of the extension study
- the second 12 weeks of the extension study
- the entire 24 weeks of the extension study and
- the combined 48 weeks of the entire study.

Safety measurements will include the following:

- Treatment-emergent AEs
- Treatment-emergent SAEs
- Treatment-emergent treatment-related AEs
- Treatment-emergent treatment-related SAEs
- Treatment-emergent AEs leading to ixazomib dose modifications
- Treatment-emergent AEs leading to early discontinuation of ixazomib
- Treatment-emergent changes in clinical laboratory measures
- Treatment emergent changes in patient vital signs
- Treatment emergent changes in UCLA SCTC GIT 2.0 questionnaire

AEs will be mapped to system organ classes and preferred terms in MedDRA. Treatment emergent events are defined as those that start or worsen after the start of study treatment through 28 days after the last dose of study treatment. AEs will be summarized by titration group, system organ class, and preferred term, and by event severity and the event's relationship to study treatment. At each level of summation, patients will be counted only once, under the greatest severity and strongest study-drug relationship.

Clinical laboratory data will be summarized at each measurement time point and for each patient's final post-baseline measurement in the following ways:

(1) with descriptive statistics (mean, standard deviation, median, and range) for eachmeasurement time point
(2) with descriptive statistics for the change from baseline in the measurements at eachpost-baseline time point; and
(3) with tables summarizing the frequencies of patients below, within, and above the normal ranges at each time point as compared with baseline. All clinical laboratory values collected during the study will be listed, with values outside the normal ranges flagged for clinical evaluation. Grade 3 and 4 laboratory results will be listed and summarized.

Vital signs will be summarized by group and listed by patient.

Data from the UCLA SCTC GIT 2.0 questionnaire at each assessment time will be summarized descriptively without imputation for missing values.

Concomitant medications will be summarized by titration group based on mapping to drug classes and generic terms in the WHO Drug Dictionary.

25.5.2 Extension Study Clinical Efficacy Analyses (see Section 24.6)

25.5.2.1 ACR CRISS (American College of Rheumatology Composite Response Index for clinical trials in early diffuse cutaneous Systemic Sclerosis)

As per Section 24.6.1, step 1 of ACR CRISS is tabulated and summarized descriptively for both treatment groups at initial study day 1, day 84 (week 12) and day 168 (week 24) of the initial study. Step 1 of ACR CRISS will be additionally tabulated and summarized descriptively for both treatment groups for extension study day 84 (week 36) and extension study day 168 (week 48).

As per Section 24.6.1, step 2 of ACR CRISS calculates changes from baseline in the predicted probability of improvement and is being applied and summarized descriptively for both treatment groups at initial study day 84 (week 12) and day 168 (week 24). Step 2 of ACR CRISS will be additionally applied and summarized descriptively for both treatment groups at extension study day 84 (week 36) and extension study day 168 (week 48).

25.5.2.2 Additional Assessments for Clinical Efficacy (see Section 24.6.2)

As per Section 24.6.2, the results of mRSS score and change from baseline for study day 84 (week 12) and day 168 (week 24) of the initial study are summarized without imputation for missing values for both treatment groups. Additional results of mRSS and change from baseline will be summarized without imputation for missing values for both treatment groups for extension study day 84 (week 36) and extension study day 168 (week 48).

As per Section 24.6.2, the percent predicted FVC and DLCO results and change from screening at study day 28 (week 4), day 56 (week 8), day 84 (week 12), day 112 (week 16), day 140 (week 20) and day 168 (week 24) of the initial study are summarized descriptively without imputation for missing values for both treatment groups. Additional percent predicted FVC and DLCO results and change from screening will be summarized descriptively without imputation for missing values for both treatment groups for extension study day 84 (week 36) and extension study day 168 (week 48).

As per Section 24.6.2, total lung capacity results and change from screening at study day 84 (week 12) and study day 168 (week 24) of the initial study are summarized descriptively without imputation for missing values for both treatment groups. Additional total lung capacity results and change from screening will be summarized descriptively without imputation for missing values for both treatment groups for extension study day 84 (week 36) and extension study day 168 (week 48).

As per Section 24.6.2, HRCT chest scan Goh scoring of ILD severity and change from baseline at initial study day 168 (week 24) are summarized descriptively for both treatment groups. HRCT chest scan Goh scoring of ILD severity and change from both baseline and initial study day 168 (week 24) will be summarized descriptively for extension study day 168 (week 48) for both treatment groups.

As per Section 24.6.2, the results for each of the disease-status scales Mahler BDI/TDI, SHAQ, PtGA and MDGA and changes from baseline at study day 84 (week 12) and study day 168 (week 24) of the initial study are summarized descriptively without imputation for missing values for both treatment groups. The results for each of these disease-status scales Mahler

BDI/TDI, SHAQ, PtGA and MDGA and changes baseline will be summarized descriptively without imputation for missing values for both treatment groups for extension study day 84 (week 36) and extension study day 168 (week 48).

25.5.3 Extension Study Post-Discontinuation Assessments for Safety

Identical to Section 24.7 Post-Discontinuation Assessments for Safety for the 24-week initial study, participants in the 24-week extension study who prematurely and permanently discontinue ixazomib study medication and continue monitoring with extension study post-discontinuation visits (see Section 25.4.2) will be included for the analysis of post-discontinuation safety data. Summaries of AEs, deaths, and patient disposition will be presented.

Safety outcome measures used will include, but will not be limited to:

- Treatment-emergent (not ixazomib) AEs
- Treatment-emergent (not ixazomib) SAEs
- Treatment-emergent (not ixazomib) treatment-related AEs
- Treatment-emergent (not ixazomib) treatment-related SAEs
- Treatment-emergent (not ixazomib) changes in clinical laboratory measures
- Treatment emergent (not ixazomib) changes in patient vital signs
- Treatment emergent (not ixazomib) changes in UCLA SCTC GIT 2.0 questionnaire

25.5.4 Extension Study Post-Discontinuation Clinical Efficacy Analysis

Participants who prematurely and permanently discontinue ixazomib study medication during the extension study and who continue monitoring with extension study post-discontinuation visits (see Section 25.4.2) will be included for the analysis of post-discontinuation clinical efficacy data.

25.5.4.1 ACR CRISS (American College of Rheumatology Composite Response Index for clinical trials in early diffuse cutaneous Systemic Sclerosis)

Step 1 ACR CRISS will be tabulated and summarized descriptively for extension study post-discontinuation visit 3 (ESPD day 84) and post-discontinuation visit 6 (ESPD day 168) as applicable and the extension study final post-discontinuation visit.

Step 2 ACR CRISS calculates changes from baseline in the predicted probability of improvement and will be applied and summarized descriptively for extension study post-discontinuation visit 3 (ESPD day 84) and post-discontinuation visit 6 (ESPD day 168) as applicable and the extension study final post-discontinuation visit.

25.5.4.2 Additional Assessments for Extension Study Post-Discontinuation Clinical Efficacy

Additional results of mRSS and change from baseline will be summarized without imputation for missing values for both treatment groups for extension study post-discontinuation visit 3 (ESPD day 84) and post-discontinuation visit 6 (ESPD day 168) as applicable and the extension study final post-discontinuation visit.

Additional percent predicted FVC and DLCO results and change from screening will be summarized descriptively without imputation for missing values for both treatment groups for extension study post-discontinuation visit 3 (ESPD day 84) and post-discontinuation visit 6 (ESPD day 168) as applicable and the extension study final post-discontinuation visit.

Additional total lung capacity results and change from screening will be summarized descriptively without imputation for missing values for both treatment groups for extension study post-discontinuation visit 3 (ESPD day 84) and post-discontinuation visit 6 (ESPD day 168) as applicable and the extension study final post-discontinuation visit.

As per Section 24.6.2, HRCT chest scan Goh scoring of ILD severity and change from baseline at initial study day 168 (week 24) are summarized descriptively for both treatment groups. HRCT chest scan Goh scoring of ILD severity and change from both baseline and initial study day 168 (week 24) for both treatment groups will be summarized descriptively for extension study final post-discontinuation visit.

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