Official Title:	A Single-Arm, Open-Label, Phase I/II Study of Glasdegib for Sclerotic Chronic Graft-vs-Host Disease
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PROTOCOL

TITLE:	A Single-Arm, Open-Label, Phase I/II Study of Glasdegib for Sclerotic Chronic Graft-vs-Host Disease
PROTOCOL NUMBER:	FH8771
STUDY DRUG:	Glasdegib (PF-04449913)
IND NUMBER:	145532
PRINCIPAL INVESTIGATOR:	Stephanie Lee, MD, MPH 1100 Fairview Ave N, D5-290 Seattle, WA 98109 Email: sjlee@fredhutch.org
COORDINATING STUDY CENTER:	Fred Hutchinson Cancer Research Center
PARTICIPATING SITES:	Duke University – Duke Cancer Institute University of Utah – Huntsman Cancer Institute
PROTOCOL VERSION HISTORY:	Version 1.3 September 9, 2019 Version 1.4 April 7, 2020 Version 1.5 July 8, 2020 Version 1.6 August 3, 2021

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STUDY ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CBC	complete blood count
CFR	Code of Federal Regulations
cGVHD	Chronic graft-versus-host disease
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria For Adverse Events
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EOT	End of treatment
FFS	failure-free survival (survival free from addition of another systemic chronic GVHD treatment, relapse or death)
GVHD	graft-versus-host disease
Hh	Hedgehog
ICF	informed consent form
IRB	institutional review board
KPS	Karnofsky Performance Status
MR	mixed response
NIH	National Institutes of Health
ORR	overall response rate (complete plus partial remission)
PD	progressive disease
PR	partial response
SAE	serious adverse event
SMO	smoothened
TdP	Torsades de pointes

STUDY SYNOPSIS

Study Title:	A Single-Arm, Open-Label, Phase I/II Study of Glasdegib for Sclerotic Chronic Graft-vs-Host Disease
Protocol Number:	FH8771
Sponsor:	Stephanie J. Lee, M.D., M.P.H.
Study Drug:	Glasdegib (PF-04449913)
Phase:	I/II
Study Centers:	3
Study Objectives:	Primary Objective: • Determine whether 50 mg daily of glasdegib is safe and tolerable in the cGVHD population. Secondary Objectives: • Determine best overall response rate by 12 months (complete response + partial response) for sclerotic manifestations of cGVHD. • Determine best overall response rate by 12 months (complete response + partial response) for all manifestations of cGVHD. • Examine the safety profile of glasdegib in the cGVHD population. • Bank blood and skin biopsy material for future biologic studies.
Study Design:	This phase I/II trial will examine the safety, tolerability and efficacy of glasdegib in cGVHD treatment. This is a single-arm, open-label study.
Dose Regimen/Route of Administration:	Glasdegib will be administered orally at a dose of 50 mg once daily for 28 days, for a total of up to 24 monthly cycles of treatment.
Safety Parameters:	Grade 3-5 adverse events and all serious adverse events will be collected.
Number of Subjects:	20
Inclusion Criteria:	1. At least 18 years old 2. Diagnosed with moderate or severe cGVHD according to the 2014 NIH Consensus Criteria 3. Diagnosed with cGVHD-related sclerosis or fasciitis

	• Skin feature score of at least 2 OR • Joints and fascia score of at least 1 4. New, stable or progressive sclerosis/fasciitis despite treatment with at least one prior line of systemic therapy for cGVHD. 5. Female patients who: • Are documented to be postmenopausal or are surgically sterile, OR • If of childbearing potential, agree to use at least 1 highly effective method of contraception from the time of signing the informed consent form through 30 days after the last dose of study drug, OR agree to practice true abstinence or exclusively non-heterosexual activity when this is in line with the preferred and usual lifestyle of the subject 6. Male patients who: • Are surgically sterile (vasectomized) OR • Agree to use at least 1 highly effective method of contraception during the entire study treatment period and through 30 days after the last dose of study drug, OR agree to practice true abstinence or exclusively non-heterosexual activity when this is in line with the preferred and usual lifestyle of the subject, AND • Agree to use a condom to prevent potential transmission of investigational drug in seminal fluid 7. Patients who meet the following clinical laboratory criteria: • Absolute neutrophil count (ANC) > 1000/μL, platelet count > 50 x 10^9/mL • ALT and AST < 2x ULN and normal total bilirubin unless attributed to cGVHD • Creatinine < 2.0 mg/dl

Exclusion Criteria:	1. Hospitalization for evaluation or management of an infection within the last 8 weeks 2. Known organ dysfunction • uncontrolled cardiovascular disease, including arrhythmias, congestive heart failure • oxygen requirement 3. Addition of any new systemic immunosuppressive treatment within the last 2 weeks. • Addition of new systemic immunosuppressive treatment along with glasdegib is also prohibited 4. QTc interval > 480 ms 5. Female patients who are lactating or have a positive serum pregnancy test 6. Major surgery within 14 days before enrollment • Does not include placement of venous access device, bone marrow biopsy, GVHD diagnostic biopsy, or other routine procedures in cGVHD or post-transplantation care 7. Use of any concomitant medications that are prohibited within the past 7 days 8. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol 9. Known intolerance to glasdegib, sonidegib, or vismodegib 10. Non-hematologic malignancy within the past 2 years with the exception of: • adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer • carcinoma in situ of the cervix or breast

	• prostate cancer of Gleason Grade 6 or less with stable prostate-specific antigen levels • cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study 11. Treatment with non-FDA approved drug within 28 days of start of this trial 12. Evidence of recurrent or progressive underlying malignant disease 13. Karnofsky performance status (KPS) < 70% 14. History of non-compliance 15. Life expectancy < 6 months 16. Grade 2 or 3 muscle cramping, or grade 1 muscle cramping that occurs at least weekly.
Concomitant Medications:	**<u>Permitted Concomitant Therapy</u>** • Ongoing systemic treatment for acute GVHD prophylaxis, acute GVHD treatment, or cGVHD treatment • Prophylaxis against infection **<u>Prohibited Concomitant Therapy</u>** • moderate/strong CYP3A4 inducers **<u>Avoid Unless No Other Alternative</u>** • moderate/strong CYP3A4 inhibitors • drugs with known risk of Torsades de Pointes • QT prolonging medications

1.0 BACKGROUND INFORMATION

1.1 CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic graft vs. host disease (cGVHD) is a major late complication of allogeneic hematopoietic cell transplantation (HCT) that affects up to 50% of HCT survivors. The syndrome is associated with major transplant-related morbidity, mortality, infectious complications, prolonged duration of immune suppression, and impaired patient-reported quality of life.[1-8] Thus, it represents a major obstacle to recovery and survival following HCT, and its prevention and treatment are of significant importance. Chronic GVHD is characterized by diverse clinical manifestations, but the most commonly affected organs are the skin, eyes, mouth, and liver.[9] However, most organs can be involved, with parallels to other systemic immune-mediated disorders.

Sclerotic GVHD is a distinctive phenotype of cGVHD that usually begins in the superficial layers of the skin and then extends to deeper layers but it may also only involve deeper structures such as fascia with normal overlying skin. Sclerotic GVHD can severely affect patients' mobility and quality of life, and it is often refractory to standard and secondary therapies. The presence of sclerosis after allogeneic HCT is considered diagnostic for cGVHD.[10] Progressive or poorly controlled sclerotic GVHD results in joint contractures, chronic skin ulcers, and pulmonary restriction, causing major disability. A prospective multicenter observational study found a cumulative incidence of 8% sclerosis with a median onset of 14 months.[11] In a large study from Fred Hutchinson Cancer Research Center, the cumulative incidence of sclerosis was 20% at 3 years. Of the patients who developed sclerosis, 13% had only skin sclerosis, 33% had only joint contracture or fasciitis, and 53% had both clinical manifestations. The development of sclerosis was associated with a reduced rate of withdrawal of immunosuppressive treatment.[12] These findings as well as clinical experience indicate that patients with sclerotic chronic GVHD have poor quality of life, often require multiple sequential therapies, and frequently exhaust available treatment options.[13-15]

1.2 CHRONIC GVHD DIAGNOSIS AND CLASSIFICATION

Diagnosis and classification of cGVHD has undergone major revision following the 2005 and 2014 NIH Consensus Conferences on Chronic GVHD. The diagnosis of cGVHD is based on the presence of diagnostic manifestations of the syndrome or distinctive manifestations supported by confirmatory biopsy or testing. Chronic GVHD severity is scored according to objective criteria for each organ involved, which is summarized by an overall global severity score of mild, moderate, or severe (Appendix 1).[10,16] Mild disease is generally well-tolerated and may sometimes be managed with topical or local therapies. Moderate and severe disease is

associated with higher mortality and requires systemic treatments.[17] Patients with moderate-severe disease and sclerosis will be enrolled in this trial.

1.3 THERAPY OF ESTABLISHED CHRONIC GVHD

Accepted standard primary therapy for cGVHD includes 0.5-1 mg/kg of prednisone or equivalent with or without a calcineurin inhibitor.[1,18,19] The addition of other systemic immune-suppressive agents to initial therapy has not provided benefit, as evidenced by trials adding azathioprine, thalidomide, hydroxychloroquine, mycophenolate mofetil and entospletinib to initial treatment with steroids.[20-23] Published primary cGVHD therapy trials demonstrate that on average 27% will achieve complete response, and 60% will achieve overall response (complete + partial response) by 6-9 months after starting initial therapy.[18,20-24] A study testing the addition of ibrutinib to standard primary therapy has almost finished accrual as of December 2018.

Based on insufficient response to primary therapy or a flare of cGVHD after tapering of initial therapy, many will go on to require additional immune-suppressive agents for cGVHD control. “Steroid-refractory” cGVHD has most commonly been defined as either progressive manifestations despite one month of treatment, or incomplete response despite two months of 1-2 mg/kg of prednisone or equivalent.[1] In addition to steroid-refractoriness, other clinical indications for additional lines of systemic immune suppressive therapy include steroid dependence and steroid intolerance. Patients with steroid-dependent cGVHD can’t tolerate tapering prednisone due to recurrent cGVHD manifestations. Steroid intolerant patients have medical complications of steroid therapy (e.g. hyperglycemia, edema, psychosis, osteoporosis), and thus require additional immune-suppressive agents to control GVHD and facilitate taper of prednisone. Multiple immune-suppressive therapies, including pharmacologic agents, monoclonal antibodies, and strategies such as extracorporeal photopheresis have demonstrated moderate activity in this setting, both ameliorating objective cGVHD manifestations, as well as facilitating taper of systemic steroids.[25] Their effectiveness is suboptimal, however, and many patients will require multiple agents to achieve disease control. A retrospective study showed that patients with cGVHD received a median of three lines of treatment and were on systemic immunosuppression for a median of 5 years. When patients stopped systemic treatment, between 30-50% of patients needed to restart treatment a median of 3-6 months later for recurrent symptoms.[26]

In August 2017, the FDA approved ibrutinib, a Bruton’s tyrosine kinase inhibitor, for the treatment of adult patients with cGVHD after failure of one or more lines of systemic immunosuppressive therapy.[27] There were 24 patients with skin involvement and an 88% response rate in skin was reported; however, skin involvement was not subclassified into

inflammatory manifestations (which usually respond to treatment) or sclerotic forms (which are much harder to treat).

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

1.4 ASSESSMENT OF THERAPEUTIC RESPONSE IN CHRONIC GVHD

Following the 2014 NIH Consensus Conference, most clinical trials use the recommended response criteria to calculate response based on change scores in nine organ-specific measures, assessed prior to study treatment and at defined points afterwards. The organ-specific change scores are used to classify responses into complete (CR, resolution of all cGVHD manifestations), partial (PR, partial resolution of cGVHD manifestations without significant worsening in any organ), stable (SD, no change in organ involvement), mixed response (MR, improvement and worsening in different organs) and progressive (PD, significant worsening in at least one organ). The overall response rate (ORR) is the CR plus PR rate.[28]

Interpretation of previously published trials for secondary cGVHD treatment is limited by a number of factors, most notably heterogeneity in response determination. In the Phase 2 ibrutinib study that led to regulatory approval (N=42), the best ORR was 67%. Adverse events were common including fatigue, diarrhea, muscle spasms, nausea and bruising.[27] The publication reported that at a median follow-up of 13.9 months, 30 (70%) had stopped treatment.

1.5 GLASDEGIB (PF-04449913, DAURISMO™)

Glasdegib (Daurismo™) is a potent and selective oral inhibitor of the Hh (Hedgehog) signaling pathway. It is FDA-approved for use in combination with low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. It is being tested for other hematologic malignancies and solid tumors.

1.5.1 Mechanism of Action

Hedgehog activation of Gli1 has been implicated in fibrotic diseases through stimulation of mesenchymal stromal cells[29] or fibroblasts to differentiate into myofibroblasts which produce collagen and fibrosis. There is growing evidence of the relevance of this pathway in systemic sclerosis[30-34] and efforts to block this pathway therapeutically using agents such as oral

hedgehog pathway inhibitors.[35] Studies in murine models of cGVHD[36] and human clinical trials of sonidegib[37] and vismodegib[38] suggest that Hh pathway inhibitors may improve fibrosis. Glasdegib binds to its target Smo (smoothened), a cell membrane protein in the Hh signaling pathway, interfering with activation of Gli1 and blocking effects of aberrant Hh signaling.

1.5.2 Safety Pharmacology

Glasdegib has been extensively characterized in nonclinical safety studies in rats, dogs and rabbits. Glasdegib was evaluated in safety pharmacology studies (cardiovascular, neurofunctional, respiratory), definitive toxicology assessments of up to 6- and 9-months duration, in vitro and in vivo genetic toxicity studies, local irritation study and embryo-fetal developmental toxicity studies. The primary target organs in rat included kidney, bone, and tooth. The primary target organs in the dog included kidney and liver. Additional observations of alopecia and skin irritation/inflammation, and QTc prolongation were identified in the dog.

In general, many findings in the rat and dog predict drug reactions reported in the clinic with glasdegib; these include muscle spasms, alopecia and QTc prolongation. However; not all the organ toxicities observed in animals have been observed in humans when treated with glasdegib. The kidney is a target organ in rat and dog. In the clinical program, at the 100 mg dose, acute kidney injury has been reported, primarily Grade 1-2. These events were often associated with prerenal confounders or consequent to or exacerbated by other glasdegib effects (e.g., diarrhea, vomiting, and/or decreased oral intake).

There have not been any liver events or significant increases in liver transaminases reported in the clinic. Findings in bone, teeth and testis are considered a potential concern only for pediatric patients, as Hh signaling is important in growth and development of these tissues. These effects have not been seen in adult patients and are not a risk for adults being treated with glasdegib.

Based on the available clinical data, the safety profile of glasdegib as a single agent administered orally on a once daily continuous dosing regimen is characterized by manageable and potentially reversible toxicities that are generally mild to moderate in severity. The key observed toxicities are: muscle spasms, dysgeusia, decreased appetite, and alopecia. Glasdegib can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Glasdegib is embryotoxic, fetotoxic, and teratogenic in animals.

For further details on the safety pharmacology of glasdegib, refer to the Investigator Brochure.

1.5.3 Drug-drug Interaction Potential

For more detailed information on drug-drug interaction potential for glasdegib, refer to the Investigator Brochure.

Please refer to Section 3.8 Concomitant Therapy for guidance on drugs that may cause drug-drug interactions.

1.6 CLINICAL EXPERIENCE – GLASDEGIB

For more detailed information on the clinical experience for glasdegib, please refer to the Investigator Brochure.

1.6.1 Clinical Efficacy

There have been no reports of the use of glasdegib for cGVHD. Glasdegib is FDA-approved at a dose of 100 mg daily in combination with low-dose cytarabine for the treatment of adult patients with acute myeloid leukemia for whom intensive chemotherapy is not an option. It is currently under investigation as treatment for hematologic and solid tumor malignancies. An ongoing Spanish study of glasdegib for sclerotic cGVHD identified 50 mg daily at the recommended dose (JA Perez Simon, personal communication). However, the Spanish study will not be sufficient to confirm the tolerability of glasdegib at this dose or provide robust efficacy data, so the present study is still warranted.

1.6.2 Adverse Events

The table below lists the most common treatment emergent/treatment-related adverse events (AE) of special interest seen thus far in 5 or more patients receiving glasdegib alone or in combination with chemotherapy (N=241). Most studies combined glasdegib with other chemotherapy making it difficult to ascertain toxicities due to glasdegib itself. Liver toxicity and neuropathy have not been identified as drug-related in the clinical program.

TABLE 2. The most common adverse events seen with glasdegib.

System Organ Class Preferred Terms	Grade 3	Grade 4	Grade 5	Total
Any AEs	**63 (26.1)**	**72 (29.9)**	**3 (1.2)**	**194 (80.5)**
Blood and lymphatic system disorders	**62 (25.7)**	**68 (28.2)**	**0 (0.0)**	**138 (57.3)**
- Anaemia	58 (24.1)	4 (1.7)	0 (0.0)	70 (29.0)
- Febrile neutropenia	59 (24.5)	6 (2.5)	0 (0.0)	65 (27.0)
- Thrombocytopenia	8 (3.3)	46 (19.1)	0 (0.0)	56 (23.2)
- Neutropenia	3 (1.2)	41 (17.0)	0 (0.0)	51 (21.2)
Nervous system disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**87 (36.1)**
- Dysgeusia	0 (0.0)	0 (0.0)	0 (0.0)	82 (34.0)
- Ageusia	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.3)
Musculoskeletal and connective tissue disorders	**11 (4.6)**	**0 (0.0)**	**0 (0.0)**	**67 (27.8)**
- Muscle spasms	8 (3.3)	0 (0.0)	0 (0.0)	52 (21.6)
- Myalgia	3 (1.2)	0 (0.0)	0 (0.0)	16 (6.6)
- Musculoskeletal pain	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.5)
Infections and infestations	**27 (11.2)**	**9 (3.7)**	**3 (1.2)**	**64 (26.6)**
- Pneumonia	9 (3.7)	2 (0.8)	1 (0.4)	15 (6.2)
- Device related infection	3 (1.2)	1 (0.4)	0 (0.0)	7 (2.9)
- Sepsis	1 (0.4)	5 (2.1)	1 (0.4)	7 (2.9)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**48 (19.9)**
- Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	48 (19.9)
Investigations	**4 (1.7)**	**0 (0.0)**	**0 (0.0)**	**17 (7.1)**
- Electrocardiogram QT prolonged	4 (1.7)	0 (0.0)	0 (0.0)	17 (7.1)
Renal and urinary disorders	**3 (1.2)**	**0 (0.0)**	**0 (0.0)**	**7 (2.9)**
- Acute kidney injury	2 (0.8)	0 (0.0)	0 (0.0)	6 (2.5)

1.6.3 Warnings and Precautions

1.6.3.1 Cytopenias

Febrile neutropenia was reported in 41% of patients being treated for myeloid malignancies, usually in combination with other chemotherapy. In patients receiving single agent glasdegib, cytopenias were reported only sporadically, with no Grade 3 / 4 events. Complete blood counts (CBC) will be monitored in this study.

1.6.3.2 QT/QTc

QTc prolongation has been observed in studies with glasdegib although usually in patients with multiple comorbidities, including significant cardiovascular medical history, and/or in patients taking concomitant therapy with QT prolonging potential. None of the events were accompanied by serious cardiac arrhythmias. Although the likelihood of QT prolongation is low, ECGs will be monitored in this study and patients with significant cardiac histories excluded.

1.6.3.3 Renal impairment

The incidence of grade 3 or higher creatinine levels was less than 5% and occurred in patients with multiple potential other contributing factors. Renal function will be monitored in this study and patients with significant baseline renal dysfunction excluded.

1.6.3.4 Muscle spasms

Muscle spasms are on-target adverse events and are considered a class effect for SMO inhibitors. No cases of rhabdomyolysis have been reported with glasdegib. In prior studies, grade 3 muscle spasms were seen in 1.2%. Patients with muscle spasms should receive adequate hydration and electrolyte imbalances should be corrected. Stretching may be helpful. Some have tried low-dose calcium channel blockers. Approximately 18% of those who had muscle cramps had ongoing symptoms at the time of treatment discontinuation, although mostly at low level.

1.6.3.5 Hyponatremia

Hyponatremia was observed in some patients, usually grade 3 or less. There was a single case of grade 4 hyponatremia that could have been related to a concurrent medication that resolved the next day. Electrolytes will be monitored in this study.

1.6.3.6 Dysgeusia

Dysgeusia is an on-target adverse event and is considered a class effect for SMO inhibitors reported in about 40% of patients, although almost always grade 1/2 and infrequently leading to treatment discontinuation. Approximately 41% of patients who had dysgeusia had ongoing symptoms at the time of treatment discontinuation.

1.6.3.7 Alopecia

Alopecia is an on-target adverse event and is considered a class effect for SMO inhibitors with 19.9% reported events, although almost always grade 1/2 and rarely leading to discontinuation. Of patients with alopecia, 75% had ongoing symptoms at the time of treatment discontinuation.

1.6.3.8 Dental effects

Loose teeth and toothache were observed in fewer than 10% patients taking glasdegib in combination with chemotherapy.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE:

Determine whether 50 mg daily of glasdegib is safe and tolerable in the cGVHD population.

2.2 SECONDARY OBJECTIVES:

2.2.1. Determine best overall response rate by 12 months (complete response + partial response) for sclerotic manifestations of cGVHD.

2.2.2. Determine best overall response rate by 12 months (complete response + partial response) for all manifestations of cGVHD.

2.2.3. Examine the safety profile of glasdegib in the cGVHD population.

2.2.4. Bank blood and skin biopsy material for future biologic studies.

3.0 STUDY DESIGN

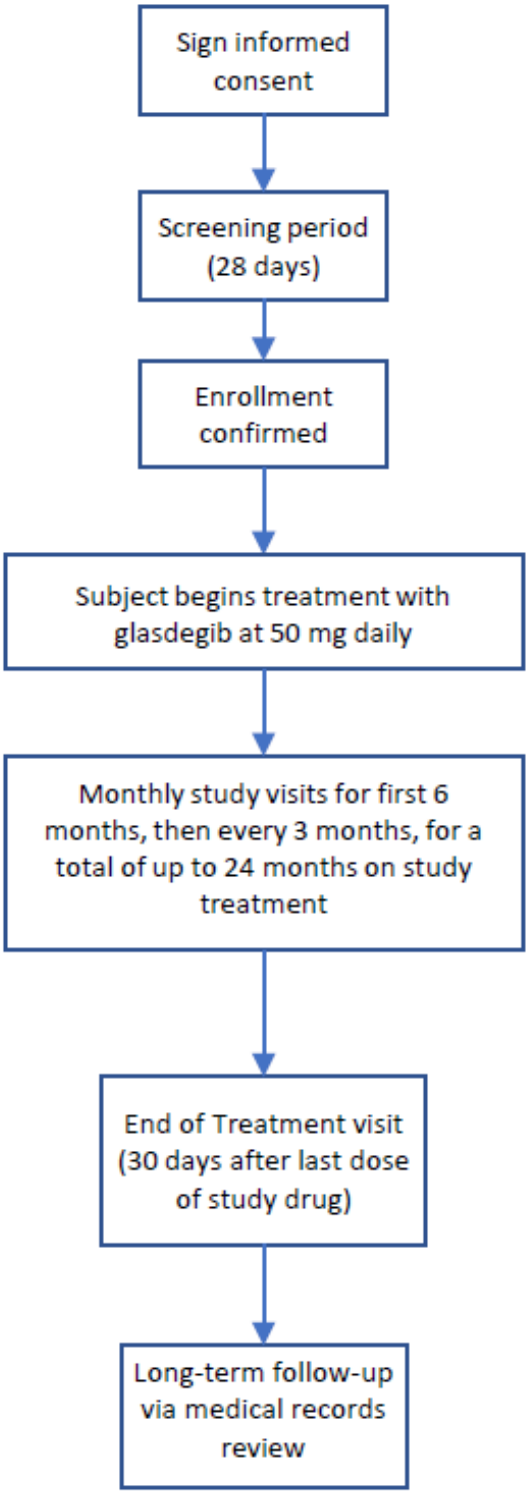
This is a single-arm, open-label, phase I/II trial examining the efficacy and safety of glasdegib 50 mg daily for treatment of sclerotic cGVHD. The FDA approved dose is 100 mg of glasdegib daily in the treatment of AML. The MTD in other glasdegib studies in healthy and cancer patients is 400 mg daily.

Twenty subjects will be enrolled. A subject is considered enrolled the day the informed consent form is signed. To control the speed of enrollment and ensure that no more than 20 subjects are enrolled across the study, each participant must be approved by the coordinating center at Fred Hutchinson Cancer Research Center prior to enrollment.

Eligible subjects will undergo up to 24 cycles of study therapy. At this point, there is no study support for longer glasdegib administration or monitoring. If study drug is discontinued prematurely, subjects will still complete remaining study assessments every 3 months through 24 months, unless they refuse continued active participation, relapse, or start a new systemic immunosuppressive treatment, in which case they are followed by chart review only. If subjects discontinue study drug within the first 6 months of study participation (prior to C7D1), they should be seen next at the time point that coincides with an overall every-3-month visit cadence (i.e. C4D1 or C7D1, whichever is next). Any monthly visits in the interim are not required for patients who have stopped glasdegib.

Refer to Appendix 2 for a comprehensive list of study assessments and their timing. The study schema is provided below (FIGURE 1).

Figure 1. Study Schema



3.1 STUDY PARAMETERS

3.1.1 Efficacy Parameters

See Section 5.5.1 for definitions.

3.1.2 Safety Parameters

The safety of glasdegib will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent grade 3 or higher AEs, any severe adverse events (SAE) or AEs leading to discontinuation of study treatment or death.

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Standard definitions for seriousness will be applied (see Section 6.1).

3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

A single arm, open-label trial is justified by the rarity of cGVHD and no prior published experience for this indication. 100 mg daily is the approved dose for acute myeloid leukemia. We will use the lower dose of 50 mg daily for 28 days to assess tolerability based on the preliminary experience of a Spanish group conducting a similar trial. Only adults will be enrolled given the lack of data in pediatric populations.

3.3 SELECTION OF STUDY POPULATION

3.3.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. At least 18 years old
2. Diagnosed with moderate or severe cGVHD according to the 2014 NIH Consensus Criteria
3. Diagnosed with cGVHD-related sclerosis or fasciitis
    - Skin feature score of at least 2 OR
    - Joints and fascia score of at least 1
4. New, stable or progressive sclerosis/fasciitis despite treatment with at least one prior line of systemic therapy for cGVHD.
5. Female patients who:
    - Are documented to be postmenopausal or are surgically sterile, OR

- If of childbearing potential, agree to use at least 1 highly effective method of contraception from the time of signing the informed consent form through 30 days after the last dose of study drug, OR agree to practice true abstinence or exclusively non-heterosexual activity when this is in line with the preferred and usual lifestyle of the subject

6. Male patients who:
    - Are surgically sterile (vasectomized) OR
    - Agree to use at least 1 highly effective method of contraception during the entire study treatment period and through 30 days after the last dose of study drug, OR agree to practice true abstinence or exclusively non-heterosexual activity when this is in line with the preferred and usual lifestyle of the subject, AND
    - Agree to use a condom to prevent potential transmission of investigational drug in seminal fluid
7. Patients who meet the following clinical laboratory criteria:
    - Absolute neutrophil count (ANC) >1000/µL, platelet count >50 x 10^9/mL
    - ALT and AST < 2x ULN and normal total bilirubin unless attributed to cGVHD
    - Creatinine < 2.0 mg/dl

3.3.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Hospitalization for evaluation or management of an infection within the last 8 weeks
2. Known organ dysfunction
    - Uncontrolled cardiovascular disease, including arrhythmias, congestive heart failure
    - Oxygen requirement
3. Addition of any new systemic immunosuppressive treatment within the last 2 weeks
    - Addition of new systemic immunosuppressive treatment along with glasdegib is also prohibited.

4. QTc interval >480 ms

5. Female patients who are lactating or have a positive serum pregnancy test

6. Major surgery within 14 days before enrollment

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

7. Use of any concomitant medications meds that are prohibited within the past 7 days

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

9. Known intolerance to glasdegib, sonidegib, or vismodegib

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

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

    - carcinoma in situ of the cervix or breast

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

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

11. Treatment with non-FDA approved drug within 28 days of start of this trial

12. Evidence of recurrent or progressive underlying malignant disease

13. Karnofsky performance status < 70%

14. History of non-compliance

15. Life expectancy <6 months

16. Grade 2 or 3 muscle cramping, or grade 1 muscle cramping that occurs at least weekly

3.3.3 Enrollment Procedures

Potentially eligible patients will be approached at participating study centers. The treating clinician will review the informed consent document with them. After the subject has signed and

dated the Informed Consent Form (ICF), screening may begin. Once all screening procedures have been completed and eligibility has been confirmed, the subject can be enrolled into the study. The screening period lasts from the date the subject signs consent until they complete the enrollment visit and start study drug, which may be up to 28 days.

Once 15 patients have been enrolled on study, the Coordinating center at Fred Hutchinson will assign screening slots to ensure that the study does not over-enroll.

3.4 STUDY DRUG

3.4.1 Premedications

No specific premedications or supporting medications are required in conjunction with glasdegib administration.

3.4.2 Formulation, Packaging, and Storage

Glasdegib tablets will be provided by Pfizer Worldwide Research and Development from clinical supply. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations. Glasdegib will be supplied as 25 mg tablets for oral administration.

Glasdegib will be packaged in high-density polyethylene bottles and should be handled with care. Each bottle will contain enough medication for the appropriate number of doses between study visits (one cycle worth dispensed at cycles 1-6, and three cycles' worth dispensed at cycles 7 and beyond), plus an additional amount to cover the allowed time windows around visit scheduling. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers and return the bottles to the site at the next study visit. Site personnel must ensure that patients clearly understand the directions for self-medication.

Investigational product should be dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.
Investigational glasdegib that will not be used (expired, returned, or leftover at end of study) should be destroyed on site according to the institution's standard operating procedure, and removal and destruction must be documented on drug accountability logs.

3.4.3 Administration of Study Drug

Glasdegib will be administered at a dose of 50 mg once daily by mouth. Up to 24 months of glasdegib treatment will be administered on study. Glasdegib is 77% bioavailable with a time to peak concentration of less than 2 hours. The drug is metabolized through the CYP3A4 pathway with a half life of 17 hours. Steady state is reached after 8 days.

At any time, patients may hold glasdegib because of side effects, toxicity or for logistic reasons. Any number of doses may be held as long as drug is resumed within 28 days. If glasdegib is held for longer than 28 days, it should not be restarted and the patient is just followed for clinical endpoints.

All protocol-specific criteria for administration of study drug must be met and documented before drug is started. Study drug will be administered or dispensed under the supervision of the investigator or identified sub-investigators. Subjects should be monitored for toxicity, and doses of glasdegib should be modified as needed to accommodate subject tolerance to treatment.

Glasdegib will be self-administered by the patient at home, unless otherwise specified. Glasdegib will be administered orally with approximately 8 ounces (240 mL) of water and should be taken in the morning, at the same time each day with or without food. Tablets must not be crushed or cut; they must be swallowed whole, not manipulated or chewed prior to swallowing. Patients should be instructed to not to take more than the prescribed dose at any time. If a patient forgets to take their dose at the regularly scheduled time, and if less than 10 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible. If more than 10 hours have passed since the scheduled dosing time, the dose should be skipped and the patient should continue on their normal dosing schedule. If a patient misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a patient vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of glasdegib.

3.4.4 Assuring Subject Compliance

Study patients will document their compliance through medication logs. The subject study drug diary is provided in Appendix 3.

3.5 STUDY TREATMENT SCHEDULE

Glasdegib will be administered at a dose of 50 mg once daily by mouth. Up to 24 months of glasdegib treatment will be administered on study.

3.6 DURATION OF THERAPY

Subjects will be treated with glasdegib for up to 24 months depending on tolerability and response.

3.7 DOSING DELAYS AND MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate glasdegib-related toxicity. If a subject experiences a treatment-related toxicity of grade 3 or higher or other intolerable treatment-related AE of any grade during the course of therapy, then glasdegib should be withheld or the dose reduced, as necessary, until the AE resolves to grade ≤ 2 or stabilizes to an acceptable degree.

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (e.g., once per week) until abnormalities have recovered to Grade ≤ 1.

Treatment with glasdegib should be withheld for any unmanageable, potentially study-drug-related toxicity that is Grade ≥ 3 in severity or for QTc greater than 500 ms. Any other clinically important events where dose delays may be considered appropriate must be discussed with the Principal Investigator. If glasdegib needs to be held for more than 28 days for a treatment-related toxicity, it should not be restarted.

3.8 CONCOMITANT THERAPY

3.8.1 Permitted Concomitant Therapy

Standard supportive care medications are permitted as per institutional standards. These include infectious prophylaxis and symptomatic management, as well as ongoing (begun prior to study enrollment) systemic and topical therapies for acute or chronic GVHD. New topical therapies for cGVHD are also permitted and will not constitute treatment failure.

3.8.2 Prohibited or Restricted Concomitant Therapy

Other investigational agents are prohibited during the course of the study. Additionally, the co-administration of glasdegib and strong CYP3A4 **inducers** is not permitted because this decreases glasdegib levels. While this situation is of less concern in the cGVHD

population than in the acute myeloid leukemia indication, we will follow the FDA-approved guidance regarding CYP3A4 inducers. A list of strong CYP3A4 inducers and inhibitors is provided in Appendix 4.

The potential exists for drug-drug interactions with CYP3A4/5 **inhibitors**, and co-administration of glasdegib in combination with moderate/strong CYP3A4/5 inhibitors is not recommended because this could lead to increased glasdegib levels. Moderate/strong CYP3A4/5 inhibitors (Appendix 4) should be used with caution and only if considered medically necessary. If a moderate/strong CYP3A4/5 inhibitor is to be initiated in addition to glasdegib, please contact the principal investigator for guidance. ECGs should be checked prior to addition of the CYP3A4/5 inhibitor and weekly afterwards x 2 weeks to ensure the QTc interval is < 500 ms. Empiric observations in healthy people and modeling simulation suggest no more than a 12 ms increase in QTc when glasdegib and a CYP3A4/5 inhibitor are combined.

The concomitant administration of glasdegib and drugs with a known risk of Torsades de Pointes (TdP) should be avoided whenever possible because the combination may increase the risk of QTc prolongation. A list of such drugs is provided in Appendix 9. Use of these drugs is not recommended unless there are no alternatives. If a TdP drug is to be initiated in addition to glasdegib, please contact the principal investigator for guidance. ECGs should be checked prior to addition of the TdP drug and weekly afterwards x 2 weeks to ensure the QTc interval is < 500 ms.

3.9 PRECAUTIONS

3.9.1 Pregnancy Prevention

In this study, male subjects who are able to father children and female subjects who are of childbearing potential will receive glasdegib, a compound which has been associated with teratogenic risk. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use at least 1 highly effective form of contraception throughout the study and for at least 30 days after the last dose of investigational product. Male subjects must, additionally, use a condom to prevent potential transmission of investigational product in seminal fluid. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected at least 1 appropriate method of contraception from the list of permitted contraception methods (see

Table 2 below) and will confirm that the subject has been instructed in its consistent and correct use. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

TABLE 2 Highly effective methods of contraception

Highly effective (failure rate <l % if used consistently and correctly)	
Low user dependency	**High user dependency**

• Progestogen-only contraceptive implant
• Intrauterine hormone releasing system (IUS)
• Intrauterine device (IUD)
• Bilateral tubal occlusion
• Vasectomized partner
	• Combined hormonal contraception (estrogen and progestogen)
	  • Oral, intravaginal, transdermal, injectable
	• Progestogen-only hormonal contraception
	  • Oral, injectable

3.9.2 Overdose Instructions

Clinical information relevant to overdose is not available. For results from nonclinical overdose studies in rats and dogs, please refer to the Investigator Brochure.

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF.

All Grade ≥3 AE's and all SAE's associated with an overdose or incorrect administration of study drug should be recorded.

In the event of subject ingestion of more than the recommended glasdegib dosage, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of glasdegib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

3.10 DISCONTINUATION OF STUDY TREATMENT

The investigator may discontinue study treatment for any subject, if, in the investigator's opinion, it is not in the subject's best interest to continue. Additionally, a subject has the right to stop study treatment at any time. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Study treatment should be discontinued if the drug is held for a treatment-related toxicity lasting > 28 days as defined above.
- Any subject who starts new systemic immunosuppressive therapy for the treatment of chronic GVHD, becomes pregnant, or is significantly noncompliant should stop study treatment.

The End of Treatment visit should occur 28 days after the last dose of study drug. Patients should be followed on the study schedule, every 3 months (see Section 3.0), unless they start a new systemic immunosuppressive treatment for cGVHD, relapse, or refuse to continue participation. Patients will continue to be followed by chart review for survival, relapse and cGVHD outcomes unless they withdraw consent.

Note that cGVHD progression itself does not require that subjects stop glasdegib unless a new systemic immune-suppressive medication is started. In some circumstances, investigators and subjects may want to continue glasdegib despite documented cGVHD progression if other options are not available.

3.11 REMOVAL FROM STUDY

Reasons for removal of a subject from the study are below. The End of Treatment visit should still be completed approximately 28 days after the last dose, if possible.

- Subject's withdrawal of consent from study
- Decision by sponsor
- Subject lost to follow-up
- Relapse of malignancy
- Death

3.12 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the Pfizer's Pharmacovigilance procedures. Adverse events, and SAEs will be reviewed internally as part of ongoing safety surveillance.

Monthly communications with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose reductions, related SAEs, and deaths).

In addition, an external DSMB will monitor the study every 6-12 months until the last patient has received 2 months of therapy, unless there are concerns that require ongoing monitoring.

While glasdegib has demonstrated safety, it has not been previously studied in cGVHD therapy after allogeneic hematopoietic cell transplantation. Current evidence suggests that mortality after initiation of cGVHD therapy may be as high as 20% at 56 days in some high-risk patient groups (Blood and Marrow Transplant Clinical Trial Network Protocol 0801). No interim analysis is planned during this trial, but there will be continuous monitoring for a stopping rule if an exact 1-sided 80% confidence interval for the true non-relapse mortality exceeds 10% -- for example, if 2 of first $\leq$ 8, 3 of first $\leq$ 15, 4 of first $\leq$ 20 experience non-relapse mortality in the first 2 months. If the true probability of non-relapse mortality is 5%, the probability of study suspension under the above rule is approximately 0.08; if the true probability is 40%, the probability of suspension is approximately 0.99, estimated from 5,000 simulations, using R version 3.5.0.

Further details of the stopping rule include the following:

- Treatment-related mortality is any death occurring while receiving study drug, or within 30 days after discontinuation of study drug, that is possibly, probably or definitely related to the drug
- Relapse or progressive disease will factor into the attribution of cause but will not automatically prevent a death from being classified as treatment-related
- For purposes of this stopping rule, the count of patients (8, 15, etc) will reflect the order in which patients start treatment
- If a DSMB review is required because the stopping rule is triggered, patients who are already enrolled and taking glasdegib may continue treatment, pending the outcome of that review. Any enrolled patient who has consented but not started study drug may not start glasdegib treatment, pending the outcome of that review.
- The DSMB may, after review, recommend to stop the trial or continue it with or without modifications.

We will also include a stopping rule for grade $\geq$3 AEs that are known to be adverse reactions to glasdegib and hedgehog inhibitor pathway class drugs, such as musculoskeletal pain, muscle spasm, QT prolongation, anorexia, nausea, diarrhea, dizziness, elevated creatinine, elevated

transaminases, and tooth problems. If the lower bound of an 80% exact binomial confidence interval is > 20%, operationally given the total sample size 20, if any 2 of the first 4 or fewer subjects or any 3 of the first 7 or fewer subjects or any 4 of the first 11 or fewer subjects or any 5 of the 15 or fewer subjects or 6 of the first 20 or fewer subjects have unacceptable toxicity or Grade 3 or higher severity AEs, then enrollment will be halted while the DSMB reviews the study. If the true probability of Grade 3 or higher AE is 5%, the probability of study suspension under the above rule is approximately 0.02; if the true probability is 40%, the probability of suspension is approximately 0.85 (probabilities estimated from 5,000 simulations, using R version 3.5.0).

Since 2 of the first 4 patients experienced grade 3 muscle cramping, the stopping rule was triggered. Of note, these 2 patients had cramping prior to enrollment. The DSMB reviewed the data and allowed enrollment to continue but with an exclusion criterion for pre-enrollment grade 2 or 3 muscle cramps, or grade 1 cramps that occur at least weekly. For the purposes of the stopping rule, we will start again with subject #5, so if 2 of the next 4 or fewer, 3 of the next 7 or fewer, 4 of the next 10 or fewer, or 5 of the next 15 have unacceptable toxicity or grade 3 or higher severity AEs, then enrollment will be halted again while the DSMB reviews the study. If the true probability of Grade 3 or higher AE is 5%, the probability of study suspension under the above rule is approximately 0.02; if the true probability is 40%, the probability of suspension is approximately 0.85 (probabilities estimated from 5,000 simulations, using R version 3.5.0).

At the recommendation of the FDA, this trial will include a futility stopping rule for overall response rate by 12 months based on Simon's two-stage design.[39] If the null hypothesis is that the true overall response rate (CR+PR) is <20% and the alternative hypothesis is that the response rate is greater than 50%, in the first stage, at least 10 patents will be accrued, and if 2 or fewer responses are observed in the first 10, the study will be suspended. Otherwise, a total of 19-20 patients will be accrued, and the null hypothesis will be rejected if 8 or more responses are observed in 19 patients. This design yields a one-sided type I error rate of 0.025 and power of 80% by minimax. The calculation used R version 3.5.0 and Simon's two-stage design from the following website: (http://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx). This stopping rule will be evaluated by the DSMB at each meeting but would not be invoked unless the first 10 patients are fully evaluable for overall response rate by 12 months, acknowledging

that that trial may be fully accrued before then. All enrolled and treated patients will be included in this futility analysis.

At the coordinating center at Fred Hutch, the study will be reviewed annually by the Consortium Data and Safety Monitoring Committee (DSMC) according to current Institutional policies. The DSMC will review accrual, unanticipated problems, SAE's, and DSMB reports.

As the Coordinating Center PI and IND holder, the Fred Hutch PI will obtain copies of all local site IRB approvals, will receive and review adverse event reports, and will disseminate that information to the appropriate committees and the DSMB. The Fred Hutch PI will also have responsibility for establishing and carrying out procedures for assessing protocol compliance, data accuracy and completeness, and full and timely reporting of safety data to outside sites.

In addition to continuous safety monitoring by the Investigators, internal monitoring will occur at each site by staff independent of the study team using monitoring plans approved by the National Cancer Institute (since all sites will be Comprehensive Cancer Centers) and reviewed by Fred Hutchinson.

The initial monitoring visit will occur no later than 6 months after the first subject has begun study treatment. Subsequent visits will occur approximately every 6-12 months while subjects are enrolling and receiving study treatment. Monitoring reports will be reviewed by the Fred Hutch PI.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 2. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand and sign the ICF approved by the institutional review board or independent ethics committee (IRB/IEC), confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information, if required by local regulations.

4.1.2 Medical History

Collect and record the subject's relevant medical history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior systemic chronic GVHD treatments also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. AEs will be recorded using CTCAE version 5.0 criteria. Important additional requirements for reporting SAEs are explained in Section 6.2.4.

4.1.4 Concomitant Medications and Therapy

Document all concomitant systemic medications and procedures from within 21 days before the start of study drug administration through 28 days after the last dose of study drug.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3.1 and 3.3.2. All screening procedures, unless otherwise indicated, should be completed within 28 days of the first dose of study drug.

4.1.6 Karnofsky Performance Status

The Karnofsky performance index is provided in Appendix 5 and must be captured at enrollment to confirm eligibility.

4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the height (screening only) and weight, blood pressure and general physical examination.

Symptom-directed and response assessment physical exams will be done during the treatment period and at the End of Study visit.

4.1.8 Serum Pregnancy Test

Pregnancy tests will be required for women of childbearing potential during screening.

4.1.9 Hematology

Hematology studies must include complete blood count (CBC) with differential, including hemoglobin, hematocrit, platelet count, and ANC.

4.1.10 Serum Chemistry

Chemistry panel must include alkaline phosphatase, ALT, creatinine, total bilirubin, sodium, potassium, magnesium.

4.1.11 Pulmonary Function Tests and Spirometry

Full pulmonary function testing is required at Cycle 1 Day 1. Only spirometry is required at day 1 of cycles 4, 7, 10, and 13, and EOT. Spirometry is required at day 1 of cycles 16, 19, and 22 if a patient has bronchiolitis obliterans syndrome or as clinically indicated.

4.1.12 Patient-Reported Outcomes

Subjects will complete the Lee Chronic GVHD Symptom Scale and the Patient-reported Outcomes Measurement Information System (PROMIS)-29 survey (See Appendix 10) at Day 1 of cycles 1, 4, 7, 10, 13, 16, 19, 22 and End of Treatment.

The Lee Chronic GVHD symptom scale (LSS) is a 30 item measure with one summary score and 7 domains: skin, mouth, eye, lung, psychoemotional, vitality and nutrition.[40,41] Higher scores indicate higher symptom burden. Scores may be calculated if more than half of items in a subscale are answered. Scores range from 0-100 with higher scores indicated greater symptom burden. A difference of 6-7 points on the summary score is considered clinically meaningful but since this scale measures cGVHD symptoms, general population norms are not available.

The PROMIS-29 contains 29 scored items and 7 subscales: for the physical and social functioning scales, higher scores indicate better functioning; for fatigue, pain, anxiety, depression, and sleep scales, higher scores indicate a higher symptom burden.[42] Similar to the SF-36, scores are normalized to 50 with a STD of 10 with higher scores indicating better functioning, and scores greater than 0.5 times STD (i.e., <45 or >55, compared to the general population) are considered clinically meaningful.

4.1.13 Clinician-Reported Outcomes

The NIH Chronic GVHD Response Assessment (Appendix 6) will be completed monthly, based on physical exam findings, testing and patient interviews. The assessment must be completed by a clinician.

4.1.14 Biologic Studies

These studies aim to discern the biologic impact of Hedgehog pathway inhibition in the treatment of cGVHD. Peripheral blood samples (20 mL in a heparinized tube and 4 mL in an EDTA tube) will be obtained on day 1 of cycles 1, 2, 4, and 7 and processed into peripheral blood mononuclear cells and plasma. Samples will be frozen and batch shipped to Fred Hutch for storage and potential study later depending on the clinical results of the trial. Four-millimeter punch biopsies will be obtained before and after 6 months of treatment with glasdegib in consenting patients. Patients may still participate in the trial if they refuse the research skin biopsies. Biopsies are bisected, with half stored in RNAlater, and half embedded in OCT (optimal cutting temperature compound), for later analysis. Skin biopsies will not be performed if there are contraindications as outlined in Manual of Operations.

4.1.15 Study Drug Accountability

Subjects will return unused medication at each study visit.

4.2 ASSESSMENT OF RESPONSE TO TREATMENT

Response assessments will be evaluated based on NIH Criteria (refer to Appendix 7).

4.3 END OF TREATMENT VISIT AND SAFETY FOLLOW-UP

An End of Treatment (EOT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason, including after completing 24 months of treatment on study. The EOT visit should be scheduled within 28 days (with +/- 7-day window) after the last dose of study drug but is not required for subjects who discontinue from the study within 10 days of a completed, scheduled study visit.

If a patient is not willing or able to return for evaluation or is seen prior to 28 days after the last dose of study medication, study staff will call the patient to document any new events occurring within 28 days of the last dose (safety follow-up).

4.4 FOLLOW-UP FOR NEW SYSTEMIC TREATMENT, DISEASE RELAPSE, AND SURVIVAL

4.4.1 Long-term Follow-up

Once subjects discontinue glasdegib and start a new systemic immunosuppressive treatment, refuse to continue participation, or are diagnosed with relapsed malignancy, they will be followed via medical record review for new systemic cGVHD treatment, disease relapse, and survival.

4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, unsafe or medically unnecessary because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned and the reason for the missed visit recorded in the database.

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

This is a Phase I/II, single-arm trial designed to assess the safety and efficacy of glasdegib in subjects with sclerotic cGVHD.

5.2 RATIONALE FOR SAMPLE SIZE

With a sample size of 20 patients, the best ORR will be estimated with an 80% exact binomial confidence intervals (CIs).[43] If glasdegib is more effective than ibrutinib, the lower bound of the CIs will be used to provide evidence that the true ORR is greater than a specific response rate. For instance, if there are 17 response (CR+PR) out of 20 patients (85%), the corresponding 80% CI will exclude 67% which is greater than the published historical chronic GVHD trials with ORR 67%. However, even if glasdegib is not statistically more effective than ibrutinib, it may still be a preferable treatment if the toxicity is less or the response rate for sclerotic features is encouraging.

5.3 ANALYSIS POPULATIONS

All efficacy and safety analysis will be performed using the treated population, which consists of all subjects who receive any amount of study treatment. The characteristics of this population will be described. The analysis of duration of response will only include subjects who have achieved objective response.

5.4 MISSING DATA HANDLING

No imputation of values for missing data will be performed except: missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of glasdegib cycles completed and the number and timing of prescribed dose delays, reductions and interruptions.

5.5.2 Analysis of Endpoints

5.5.2.1 Primary Endpoint

The primary endpoint is the safety and tolerability of glasdegib in the cGVHD population. This will be reported as the type and severity of adverse events, severe adverse events and number of cycles completed and reasons for discontinuation.

5.5.2.2 Secondary Endpoints

The secondary endpoints are best overall Response Rate (ORR) in sclerotic manifestations, best ORR in all cGVHD manifestations, and safety.

Overall Response Rate (ORR) in sclerotic manifestations

Best ORR of sclerotic manifestations by 12 months after the initiation of glasdegib and before another systemic immunosuppressive regimen is started represents the composite outcome of complete and partial response (CR + PR). ORR will be calculated according to (1) the response definitions of the NIH Consensus Conference for (a) skin or joint scores (0-3), where improvement by at least 1 point is a PR and return to score 0 is a CR, or (b) the photographic range of motion scale (0-25) where improvement by at least 1 point is a PR and return to score 25 is a CR; and (2) change in the 0-10 sclerotic severity scale where at least a 2 point improvement is a PR or return to 0 (CR).

Overall Response Rate (ORR) in all cGVHD manifestations

Best ORR of all cGVHD manifestations by 12 months after the initiation of glasdegib and before another systemic immunosuppressive regimen is started represents the composite outcome of complete and partial response (CR + PR). ORR will be calculated according to the response

definitions of the NIH Consensus Conference. ORR both including and excluding skin sclerotic features will be reported.

Safety

Safety assessments will consist of monitoring and recording adverse events. See section 6.0 below.

In addition, we will describe the following exploratory endpoints:

Failure-Free Survival

This endpoint will be estimated at 12 months with events considered death, relapse, or start of another systemic immunosuppressive agent. Patients lost to follow-up or who withdraw consent will be censored.

Patient-reported outcomes

Subjects will provide assessments of their symptom burden and quality of life using a validated instrument recommended by the NIH Consensus on Chronic GVHD (Lee Chronic GVHD Symptom Scale) and the NIH-endorsed PROMIS-29 (See Appendix 10). These will be collected before starting glasdegib on day 1 of cycle 1, and again on D1, cycles 4, 7, 10, 13, 16, 19, 22 and EOT. Scores will be calculated for each instrument based on published algorithms with absolute changes from baseline and clinically meaningful changes described for the population as a whole and based on CR+PR vs. SD+MR+PD.

Biologic studies

These studies aim to discern the biologic impact of Hedgehog pathway inhibition in the treatment of cGVHD and may include the following skin assays as well as others: expression of Shh, Gli1, Gli2, ptch-2, collagen, TGFb, and Smo. Immunohistochemistry may be performed for Patched, Shh, Snail, GSK3-β, β-catenin, or Ihh as well as other markers.

6.0 SAFETY MONITORING

6.1 DEFINITIONS

Adverse Event

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

Unexpected Adverse Event

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

Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities. A serious adverse event (SAE) is any adverse event, without regard to causality, that includes any of the following:

- Death
- A life-threatening adverse event (places the subject at an immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacitation (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly or birth defect
- Is a **medically important event**. This refers to an AE that, in the medical judgment of the Principal Investigator, may jeopardize the subject, or may require medical or surgical intervention to prevent one of the outcomes listed above.

A planned medical or surgical procedure is not, it itself, an SAE.

6.1.1 Severity

The study site will grade the severity of adverse events experienced by study participants according to CTCAE version 5.0. Grade 1 and grade 2 adverse events do not require reporting in this study. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The study will collect all Grade 3 and above adverse events, regardless of relationship to study therapy or study procedures, unless the event is one of the exceptions listed below. Severity grading will be based on CTCAE version 5.0. Grade 1 and 2 events will not be collected.

The following will NOT be collected as adverse events:

- An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline. Any laboratory value meeting seriousness criteria must also be reported.
- Manifestations of chronic GVHD will not be collected as AE's unless they meet seriousness criteria.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

Non-serious, Grade 3 and above adverse events must be recorded in the database within 20 days of becoming aware of the event. Non-serious adverse events collected in the database will be compiled by the coordinating center and reported to the DSMB at regularly scheduled meetings.

Reporting procedures: All serious adverse events must be reported to Pfizer within 24 hours of first awareness of the event. If the event is fatal or life-threatening, it must be reported immediately. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available. Sites must notify the coordinating center at Fred Hutchinson, and the study staff at Fred Hutchinson will prepare the report for Pfizer. Reports will be submitted on the Pfizer-provided *Investigator-Initiated Research Serious Adverse Event Report Form*, and faxed to Pfizer along with the *Reportable Event Fax Cover Sheet*. The Sponsor-Investigator at Fred Hutchinson will determine whether the event meets the criteria for expedited reporting, and will prepare the IND Safety Report as necessary. Significant and relevant follow-up information should also be reported to Pfizer as soon as

possible. Fred Hutchinson and the sites will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study drug and ends with the EOT visit, or 28 days after the last dose of study drug, whichever is later. Exception to this reporting period are (a) any AE occurring due to a protocol-specific screening procedure; and (b) if any SAE occurs beyond 28 days after the last dose of glasdegib ***AND*** it is assessed by the investigator as possibly related to glasdegib, it must be reported as an SAE.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE CRF.

Each recorded AE or SAE will be described by its diagnostic term, duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements (FDA Guidance 2012).

See Appendix 8 for more detail on assessing relationship.

6.2.3 Pregnancy, lactation, and occupational exposure

Even though there may not be an associated SAE, exposure to glasdegib during pregnancy, exposure during lactation, and occupational exposure are all reportable, and reporting procedures should follow those for SAEs.

All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 30 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

6.2.4 Hy's Law Cases

Cases of potential drug-induced liver injury as assessed by laboratory values are also reportable to Pfizer as SAEs. If a study subject develops abnormal values in AST and/or ALT, concurrent with abnormal elevations in total bilirubin and no other known cause of livery injury, that event is classified as a Hy's Law Case and must be reported.

6.2.5 IND Safety Reporting

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

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

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

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

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

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

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

The Sponsor retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity

- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

The investigator, or designee, must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21 Code of Federal Regulations (CFR) Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with regulatory agencies and IRBs/IECs. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.2 RECORD RETENTION

The investigators and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information, subject files (source documentation) that substantiate database entries, all relevant correspondence and other documents pertaining to the conduct of the study.

The investigator shall retain study records in accordance with institutional and/or national/local regulations, whichever is longer.

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Appendix 1. NIH Global Severity of Chronic GVHD

Mild chronic GVHD

1or 2 organs involved with no more than score 1 *plus*
Lung score 0

Moderate chronic GVHD

3 or more organs involved with no more than score 1

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

Severe chronic GVHD

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

Key points:

1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Appendix 2. Schedule of Assessments

	SCR	C1D1	C1D8	C1D 15, 22	C2D1	C2D15	C3D1	C4D1	C5D1	C6D1	C7D1	C10D1, C13D1, C16D1, C19D1, C22D1	EOT
Visit Windows	-28 days	-7 days*	+/- 3 days			+/- 7 days							
Signed informed consent	X												
Confirm eligibility	X												
Physical exam and GVHD evaluation	X	X			X		X	X	X	X	X	X	X
Clinical labs[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test[2]	X												
Electrocardiogram[5]	X	X	X		X		X	X	X	X	X	X	
Research blood samples[5]		X			X			X			X		
Skin biopsy		X									X		
Pulmonary function test		X											
Spirometry[5]								X			X	X[4]	X
Patient-reported outcomes[3]		X						X			X	X	X
Chronic GVHD Provider Assessment		X			X		X	X	X	X	X	X	X
Dispense glasdegib study drug		X			X		X	X	X	X	X	X	

[1] Clinical labs to include CBC, ALT, AlkPhos, Total bilirubin, Creatinine, Sodium, Potassium, Magnesium. Verify that creatine kinase is normal prior to first dose.
[2] Serum pregnancy test required for women of childbearing potential **within -7 days of C1D1**.
[3] Patient-reported outcomes to include: Lee Chronic GVHD Symptom Scale and PROMIS-29 (Appendix 10)
[4] Spirometry required for cycles 10 and 13. Spirometry at cycles 16, 19, 22 is required only if a patient has BOS, otherwise as clinically indicated
[5] Not required for patients who have discontinued glasdegib. (Spirometry is still required at EOT, unless it has already been done within the past 3 months.)

*Everything within this column can be done within the 7 days prior to the first dose, or on the actual Day 1. Do not need to repeat physical exam, clinical labs, or ECG if done within -7 days for screening. In all cases, study staff will check in with the patient by phone or in person within 48 hours prior to the first dose in order to confirm that there have been no significant changes to the patient's GVHD or overall health.

Target visit dates will be calculated based on a 28-day treatment cycle, and with C1D1 as the starting date.

End of Treatment (EOT) visit should occur 28 days (+/- 7 days) from last dose of study drug.

Appendix 3. Subject Drug Diary

FH 8771 Glasdegib for Sclerotic GVHD

Glasdegib Study Participant Self-Administration Diary

Subject ID:		Cycle #:	
Assigned dose:	50 mg daily	Date Dispensed:	

INSTRUCTIONS:

Storage:

Keep the study drug (glasdegib) at room temperature. It should be stored according to the storage conditions as indicated on the label.

Dosing:

Take your study medication once daily, in the morning, at about the same time. You should take it with a glass of water, and you may take it with or without food.

The tablets must be swallowed whole. Do NOT try to break them, chew them, or dissolve them in water.

If you miss a dose, you can take it up to 10 hours after the scheduled time with a return to the normal schedule at the next dose. If it has been more than 10 hours, do not take the missed dose. Take the next dose as the scheduled time. Do not take extra tablets to make up the missed dose. If you vomit at any time after taking glasdegib, do not take an extra dose. Simply take the next day's dose as scheduled.

Please bring the bottle(s) and all unused tablets to the clinic at each visit (even if the bottle is empty).

Diary:

Please record all entries in **INK.** Correct mistakes with single-line strikethrough, initials and date.

Please complete the form every day. This form will help you keep track of your study treatment doses.

If you miss a dose, write the reason. If you have any abnormal symptoms while taking the study drugs, record them on the form.

*** PLEASE BRING THIS FORM AND YOUR BOTTLES OF STUDY DRUG TO EACH VISIT***

Version 23JUL2019

Day	Date	Time	Number of tablets taken	Reason for missed or changed dose/Abnormal symptoms/Comments (if any)
Example	*01-Jan-2019*	*8 am*	*1*	*none*
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Subject signature: _____ Date: _____

Reviewed by: _____ Date: _____

Version 23JUL2019

Appendix 4. Known Strong in Vivo Inhibitors or Inducers of CYP3A

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[d]
boceprevir	carbamazepine[e]
clarithromycin[b]	phenytoin[e]
conivaptin[b]	rifampin[e]
indinavir	St John's wort[e]
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[c]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

a. A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. Withdrawn from the United States market because of safety reasons.
d. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.
e. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Sponsor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers . Web link Accessed 11 June 2015: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix 5. Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

References:

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Appendix 6. NIH Response Assessment

Glasdegib for Sclerotic Chronic GVHD

Response Assessment
Provider Survey

Instructions:

Please score all signs and symptoms. If you believe the sign or symptom is **DEFINITELY NOT** related to chronic GVHD (e.g., C difficile diarrhea, shingles rash, shortness of breath due to pulmonary embolus) then you should STILL score it but indicate the true diagnosis.

Subjective symptoms can be scored. For example, joint tightness can be scored based on subjective findings despite the absence of objective limitations.

Please score signs and symptoms present in the *last week*.

Date of Visit: _____

Subject ID: _____

Your Name: _____

Current Visit: _____

Target Date for Next Visit: _____

SKIN & ROM

	0	1	2	3
Skin *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	❑ No BSA involved	❑ 1-18% BSA	❑ 19-50% BSA	❑ >50% BSA
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Skin Features Score	❑ No sclerotic features		❑ Superficial sclerotic features "not hidebound" (able to pinch)	*Check all that apply* ❑ Deep sclerotic features ❑ "Hidebound" (unable to pinch) ❑ Impaired mobility ❑ Ulceration

If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____

How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible:

0 1 2 3 4 5 6 7 8 9 10

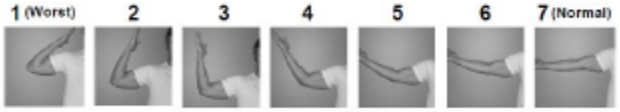
Symptoms not at all severe — Most severe symptoms possible

Please circle this person's current ROM for each joint below:

Shoulder

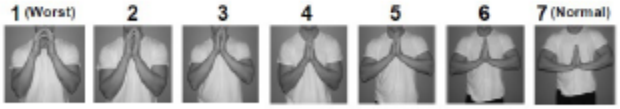
❑ Not done

Elbow



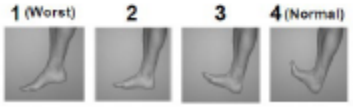
❑ Not done

Wrist/finger



❑ Not done

Ankle



❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

		0	1	2	3
Mouth		❑ No symptoms	❑ Mild symptoms with disease signs but not limiting oral intake significantly	❑ Moderate symptoms with disease signs with partial limitation of oral intake	❑ Severe symptoms with disease signs on examination with major limitation of oral intake
		☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Mouth	**Ulcers**	❑ None (=+0)		❑ Ulcers involving (≤20%) (=+3)	❑ Severe ulceration (> 20%) (=+6)
	Erythema	❑ None	❑ Mild erythema OR Moderate erythema (<25%)	❑ Moderate (≥25%) OR Severe erythema (<25%)	❑ Severe erythema (≥25%)
	Lichenoid	❑ None	❑ Lichen-like changes (<25%)	❑ Lichen-like changes (25-50%)	❑ Lichen-like changes (>50%)
		Total score for all mucosal changes			
GI Tract *Check all that apply:* o Esophageal web / proximal stricture or ring o Dysphagia o Anorexia o Nausea o Vomiting o Diarrhea o Weight loss ≥5% over past 3 months o Failure to thrive		❑ No symptoms	❑ Symptoms without significant weight loss (<5%) over past 3 months	❑ *Check all that apply* O Symptoms associated with mild to moderate weight loss (5-15%) over past 3 months O Moderate diarrhea without significant interference with daily living	❑ *Check all that apply* O Symptoms associated with significant weight loss >15% over past 3 months, requires nutritional supplement for most calorie needs O Esophageal dilation O Severe diarrhea with significant interference with daily living
		❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Esophagus		❑ No symptoms	❑ Occasional dysphagia or odynophagia with solid food or pills during the past week	❑ Intermittent dysphagia or odynophagia with solid food or pills, but not for liquids or soft foods during the past week	❑ Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week
		❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Upper GI		❑ No symptoms	❑ Mild, occasional symptoms, with little reduction in oral intake during the past week	❑ Moderate, intermitted symptoms, with some reduction in oral intake, during the past week	❑ More severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the week
		❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			

	0	1	2	3
Lower GI ❑ **Diarrhea**	❑ No loose or liquid stools during the past week	❑ Occasional loose or liquid stools on some days during the past week	❑ Intermittent loose or liquid throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion	❑ Voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Eye	❑ No symptoms	❑ Mild dry eye symptoms not affecting ADL (requiring eye drops ≤3x per day)	❑ Moderate dry eye symptoms partially affecting ADL **WITHOUT** new vision impairment due to KCS *Check all that apply* ○ Requiring lubricant eye drops >3x per day ○ Punctual plugs	❑ Severe dry eye symptoms significantly affecting ADL *Check all that apply* ○ Special eyewear to relieve pain ○ Unable to work because of ocular symptoms ○ Loss of vision due to kerato-conjunctivitis sicca
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Joints /Fascia	❑ No symptoms	❑ *Check all that apply* ○ Mild tightness of arms or legs ○ Mild decreased range of motion (ROM) **AND** not affecting ADL	❑ *Check all that apply* ○ Tightness of arms or legs ○ Joint contractures ○ Erythema thought due to fasciitis ○ Moderate decrease ROM **AND** mild to moderate limitation of ADL	❑ Contractures WITH significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Genital Tract ❑ **Not Examined**	❑ No signs	❑ Mild signs and females with or without discomfort on exam	❑ Moderate signs and may have symptoms with discomfort on exam	❑ Severe signs with or without symptoms
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Lung	❑ No symptoms	❑ Mild symptoms (shortness of breath after climbing one flight of steps)	❑ Moderate symptoms (shortness of breath after walking on flat ground)	❑ Severe symptoms (shortness of breath at rest; requiring O_2)
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			

Note: Liver and pulmonary function tests are collected via chart review to calculate those scores

OVERALL STATUS

Please rate the severity of this person's chronic GVHD (Global)	
on this scale →	❑ No GVHD (0) ❑ Mild (1) ❑ Moderate (2) ❑ Severe (3)
and on this scale → *(circle one)*	cGVHD symptoms are not at all severe ← 0 1 2 3 4 5 6 7 8 9 10 → cGVHD symptoms are most severe possible

Current GVHD Status	❑ Complete response (1)	❑ Partial response (2)	❑ Mixed response (3)	❑ Unchanged (4)	❑ Progressive (5)

Since the screening visit on _____, how would you say this patient's chronic GVHD has changed?							
	Very much better (+3)	Moderately better (+2)	A little better (+1)	About the same (0)	A little worse (-1)	Moderately worse (-2)	Very much worse (-3)
cGVHD Overall	❑	❑	❑	❑	❑	❑	❑
What are your reasons for how you rated "chronic GVHD overall"? *Write in* →				(For example, has a specific organ or symptom improved or worsened?)			

Other complications related to chronic GVHD:					
	Never (0)	Past, not now (1)	Mild (2)	Moderate (3)	Severe (4)
1. Ascites (serositis)	❑	❑	❑	❑	❑
2. Pericardial Effusion	❑	❑	❑	❑	❑
3. Pleural Effusion(s)	❑	❑	❑	❑	❑
4. Nephrotic syndrome	❑	❑	❑	❑	❑
5. Myasthenia Gravis	❑	❑	❑	❑	❑
6. Peripheral Neuropathy	❑	❑	❑	❑	❑
7. Polymyositis	❑	❑	❑	❑	❑
8. Weight loss >5% without GI symptoms	❑	❑	❑	❑	❑
9. Eosinophilia >500/ul	❑	❑	❑	❑	❑
10. Platelets <100,000/ul	❑	❑	❑	❑	❑
11. Other, please specify: a. _____	❑	❑	❑	❑	❑

Clinician Signature: _____ Date: _____

Appendix 7. Response Determination

Response determination for chronic GVHD clinical trials based on clinician assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified Oral Mucosa Rating Score 0 after previous involvement	Decrease in NIH Modified Oral Mucosa Rating Score of 2 or more points	Increase in NIH Modified Oral Mucosa Rating Score of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of one or more	Decrease by 50%	Increase by 2x ULN
Lungs	-Normal %FEV1 after previous involvement -If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	-Increase by 10% predicted absolute value of %FEV1 -If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	-Decrease by 10% predicted absolute value of %FEV1 -If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and Fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least one measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0–10 scale	Clinician overall severity score increases by 2 or more points on a 0–10 scale

Appendix 8. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug? No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix 9. Drugs with a Known Risk of Torsades de Pointes

Generic Name	Drug Class	Therapeutic Use
Amiodarone	Antiarrhythmic	Arrhythmia
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Anti-cancer	Cancer (leukemia)
Azithromycin	Antibiotic	Bacterial infection
Bepridil	Antianginal	Angina pectoris
Chloroquine	Antimalarial	Malaria
Chlorpromazine	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Antibiotic	Bacterial infection
Citalopram	Antidepressant, SSRI	Depression
Clarithromycin	Antibiotic	Bacterial infection
Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Antiarrhythmic	Arrhythmia
Dofetilide	Antiarrhythmic	Arrhythmia
Domperidone	Antiemetic	Nausea, vomiting
Donepezil	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Antiarrhythmic	Arrhythmia
Droperidol	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Antiarrhythmic	Arrhythmia
Fluconazole	Antifungal	Fungal infection
Halofantrine	Antimalarial	Malaria
Haloperidol	Antipsychotic	Schizophrenia, agitation
Hydroquinidine	Antiarrhythmic	Arrhythmia
Hydroxychloroquine	Antimalarial, anti-inflammatory	Malaria, SLE, rheumatoid arthritis
Ibutilide	Antiarrhythmic	Arrhythmia
Levofloxacin	Antibiotic	Bacterial infection
Levomepromazine (methotrimeprazine)	Antipsychotic	Schizophrenia
Levosulpiride	Antipsychotic	Schizophrenia
Methadone	Opiate	Narcotic dependence, pain
Moxifloxacin	Antibiotic	Bacterial infection
Ondansetron	Antiemetic	Nausea, vomiting
Oxaliplatin	Anti-cancer	Cancer
Papaverine HCl (Intra-coronary)	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Antipsychotic	Tourette's Disorder
Procainamide	Antiarrhythmic	Arrhythmia
Propofol	Anesthetic, general	Anesthesia
Quinidine	Antiarrhythmic	Arrhythmia
Roxithromycin	Antibiotic	Bacterial infection
Sevoflurane	Anesthetic, general	Anesthesia

Sotalol	Antiarrhythmic	Arrhythmia
Sulpiride	Antipsychotic, atypical	Schizophrenia
Sultopride	Antipsychotic, atypical	Schizophrenia
Terlipressin	Vasoconstrictor	Septic shock
Terodiline	Muscle relaxant	Bladder spasm
Thioridazine	Antipsychotic	Schizophrenia
Vandetanib	Anti-cancer	Cancer (thyroid)

Source: crediblemeds.org, Drugs with Known TdP Risk, accessed 7-April-2020.

Appendix 10. Patient-Reported Outcomes

Glasdegib for Sclerotic Chronic GVHD

Response Assessment
Patient Survey

Date of Visit: _____

Study Time Point: _____

Subject ID: _____

Subject Name: _____

Lee Symptom Scale

By circling one (1) number per line, please indicate how much you have been bothered by the following problems in the past 7 days:

SKIN:	Not at all	Slightly	Moderately	Quite a bit	Extremely
1. Abnormal skin color.....	0	1	2	3	4
2. Rashes.....	0	1	2	3	4
3. Thickened skin.....	0	1	2	3	4
4. Sores on skin.....	0	1	2	3	4
5. Itchy skin.....	0	1	2	3	4
EYES AND MOUTH:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6. Dry eyes.....	0	1	2	3	4
7. Need to use eye drops frequently..	0	1	2	3	4
8. Difficulty seeing clearly.....	0	1	2	3	4
9. Need to avoid certain foods due to mouth pain.....	0	1	2	3	4
10. Ulcers in mouth.....	0	1	2	3	4
11. Receiving nutrition from an intravenous line or feeding tube....	0	1	2	3	4
BREATHING:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12. Frequent cough.....	0	1	2	3	4
13. Colored sputum.....	0	1	2	3	4
14. Shortness of breath with exercise..	0	1	2	3	4
15. Shortness of breath at rest.....	0	1	2	3	4
16. Need to use oxygen.....	0	1	2	3	4
EATING AND DIGESTION:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17. Difficulty swallowing solid foods....	0	1	2	3	4
18. Difficulty swallowing liquids.....	0	1	2	3	4

19. Vomiting.....	0	1	2	3	4
20. Weight loss.....	0	1	2	3	4
MUSCLES AND JOINTS:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21. Joint and muscle aches.....	0	1	2	3	4
22. Limited joint movement.....	0	1	2	3	4
23. Muscle cramps.....	0	1	2	3	4
24. Weak muscles.....	0	1	2	3	4
ENERGY:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25. Loss of energy.....	0	1	2	3	4
26. Need to sleep more/take naps.....	0	1	2	3	4
27. Fevers.....	0	1	2	3	4
MENTAL AND EMOTIONAL:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28. Depression.....	0	1	2	3	4
29. Anxiety.....	0	1	2	3	4
30. Difficulty sleeping.....	0	1	2	3	4

PROMIS–29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
H7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Fatigue

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Sleep Disturbance

	In the past 7 days…	Very poor	Poor	Fair	Good	Very good
Sleep100	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep110	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Ability to Participate in Social Roles and Activities

		Never	Rarely	Sometimes	Usually	Always
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER45_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Pain Interference

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Pain Intensity

	In the past 7 days…											
Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst pain imaginable