Amendment

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** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

Abbreviated Title: Pomalidomide for cGvHD
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Title: A Randomized Phase 2 Single-Center Study of Pomalidomide for Chronic GVHD

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Drug Name:	Pomalidomide
IND Number:	115336
Sponsor:	Center for Cancer Research
Manufacturer:	Celgene Protocol tracking number: PO-GvHD-NCI-0046

PRÉCIS

Background:

- Chronic graft-versus-host disease (cGvHD) is the leading cause of non-relapse morbidity and mortality in persons after allogeneic hematopoietic cell transplants.
- About 50% of persons with cGvHD have disease refractory to systemic corticosteroids and there is no standard second-line therapy.
- Thalidomide, a drug with immune-modulating effects, was active in advanced cGvHD but was difficult to use at appropriate doses.
- Pomalidomide is related to thalidomide but with higher potency and more favorable toxicity profile. It is active in multiple myeloma and myeloproliferative neoplasm–associated myelofibrosis. Preliminary data in humans with cGvHD are encouraging but data are limited.

Objective:

- Primary: Determine whether pomalidomide is effective in persons with moderate or severe cGvHD not controlled by corticosteroids.

Eligibility:

- Inclusion Criteria
  - Moderate or severe cGvHD per NIH criteria
  - Age 18 to 75 years old
  - Karnofsky performance score $\geq$60%
  - Has cGvHD that did not respond to high-dose corticosteroids (average 0.5 mg/kg/d prednisone for $\geq$8 weeks) or second-line therapy
  - Receiving stable or tapering doses of systemic therapy in the preceding 4 weeks
  - Agree to adhere to methods of contraception and other fertility control measures as prescribed by the protocol

- Exclusion Criteria
  - Acute GvHD (classic and late per NIH criteria)
  - Absolute neutrophils $<1.0 \times 10^9$/L, platelets $<75 \times 10^9$/L, estimated creatinine clearance <50 mL/min/1.73m^2
  - NIH lung score 3
  - Pregnant or lactating
  - Uncontrolled infection

Design:

Randomized phase 2 trial with the single stage selection design. Patients will receive either a constant low dose of pomalidomide (0.5 mg/day) for six months or a strategy of increasing dose of pomalidomide from 0.5 mg/d up through each individual patients' maximum tolerated dose, with escalations by 0.5 mg/d every 2 weeks to a maximum of 2.0 mg/d. As an early stopping rule for futility, if after 7 patients have enrolled on either arm, 0 have responded, then no further patients will be accrued to that arm as soon as this can be determined. To protect patient safety, an early stopping rule will be implemented. With two arms, each of which has a maximal accrual

of 16 patients, up to 32 evaluable patients will be randomized. Response assessments will occur every 3 months with primary efficacy endpoint evaluated at 6 months. Patients with responding disease will continue therapy for another 6 months.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

1.1.2 Determine whether pomalidomide is effective in persons with moderate or severe chronic graft-versus-host disease (cGvHD) not controlled by corticosteroids.

1.1.3 Secondary Objectives:

1.1.3.1 Determine whether pomalidomide is safe in persons with moderate or severe cGvHD not controlled by corticosteroids.

1.1.3.2 Determine the immune-modulatory effects of pomalidomide in persons with moderate or severe cGvHD.

1.1.3.3 Determine limited pharmacokinetics after oral administration of pomalidomide.

1.2 BACKGROUND AND RATIONALE

1.2.1 Chronic Graft-Versus-Host Disease

cGvHD is an important late complication of allogeneic hematopoietic cell transplantation. It is a leading cause of mortality in persons more than 2 years post transplant.[1,2] Symptoms of cGvHD usually appear within 2 years post transplant. Incidences range from 6%-80% depending on recipient age, donor type (related or unrelated, HLA matched or mismatched), graft type (blood, bone marrow or umbilical cord), graft manipulation or donor lymphocyte infusions.[3] Chronic GvHD is strongly associated with prior acute GvHD (aGvHD).[4,5] Traditionally the cutoff point between aGvHD and cGvHD was day 100 post transplant. In 2005 an NIH consensus project proposed two main GVHD categories, each with two subcategories: (1) "classic" aGvHD occurring within 100 days post transplant and (2) "persistent, recurrent or late" aGvHD. The broad category of cGvHD includes: (1) "classic" cGvHD (without features or characteristics of aGvHD) and (2) an "overlap syndrome" with concordant features of cGvHD and aGvHD.[3] cGvHD is a multi-organ alloimmune and autoimmune disorder characterized by immune dysregulation, immunodeficiency, impaired organ function and decreased survival. It requires prolonged ongoing immunosuppression and inter-disciplinary management.

1.2.1.1 Pathophysiology

The pathophysiology of cGvHD is poorly understood. T- (both Th1 and Th2) and B-cells play a role in the pathogenesis of cGvHD, suggesting a general loss of tolerance, including abnormalities in the function of regulatory T-cells (Tregs). Natural Tregs (CD4+,CD25+,FoxP3+) maintain self-tolerance.[6] Studies in mice indicate Tregs can suppress GvHD and that a deficiency of Tregs worsens GHD.[7] There are conflicting data in humans concerning role of Tregs in the development of cGvHD.[8] A recent study suggested *in vivo* administration of low-dose IL-2 as a potential Treg-mediated therapeutic approach for severe cGvHD.[9]

Several studies suggested that aGvHD is associated with predominant Th1-type immune response and cGvHD with Th2-type immune response. Th1 cells produce interferon- γ (IFN-γ)

that mediates cell immunity, and Th2 cells produce interleukin (IL)-4, IL-5 and IL-13, which mediate humoral immunity. Following T-cell dysregulation, there is consequently cytokine dysregulation. In persons with cGvHD, higher levels of tumor necrosis factor-α, IL- 6, transforming growth factor-β, IL-1β and lower levels of INF-γ and IL-10 are reported.[1,10-13]

Autoimmunity and autoreactive T-cells have an important role in cGvHD. Some studies have shown that host thymus is not required for induction of cGvHD and that quiescent autoreactive T- and B-cells in transplants from non-autoimmune donors may be activated and expanded to cause cGvHD.[14] In contrast, involvement of thymus-dependent pathways in cGvHD development begins with injury to the thymus from a chemotherapy-conditioning regimen or aGvHD, leading to loss of B-cells with their ability to produce antibodies and to present antigen, which may enhance development of cGvHD. Autoantibodies like anti-nuclear, anti-mitochondrial, anti-parietal, anti–smooth muscle and anti–parotid are present in persons with cGvHD.[15,16] Also, persons with autoantibodies had more cGvHD-associated symptoms than persons without autoantibodies.[15] Autoantibodies against platelet-derived growth factor receptor (PDGFR) may play a role in cGvHD.[17] These PDGFR-α autoantibodies stimulate thyrosine phosphorylation in a cascade of events contributing inflammation and fibrosis.

The studies report elevated levels of BAFF (B-cell activating factor of the TNF family), which is produced by T-cells and granulocytes. BAFF supports differentiation and survival of normal B-cells in persons with cGvHD and autoimmune diseases.[7,18] Fuji et al. showed that in early-onset cGvHD, there are elevated sBAFF, sIL-2Rα, sCD13, and anti-dsDNA levels. In late-onset cGvHD, sBAFF, anti-dsDNA and ANA are higher, suggesting that the B-cell activation is predominant.[19] These observations create rationale for treatments with anti-CD20 antibodies in cGvHD.[20]All of these pathways are potential targets for cGvHD therapy. However, to date no laboratory parameter is considered a reliable biomarker for the diagnosis, measurement of severity, prognosis or therapeutic effect in cGvHD.

1.2.1.2 Clinical Manifestations

The usually affected organs in cGvHD are the skin, eyes, mouth, gut, liver, lungs, joints and genitourinary tract. Examples of diagnostic skin manifestations are sclerotic features and poikiloderma, lichen-type and hyperkeratotic plaques in the mouth or bronchiolitis obliterans in lung biopsy.[3] The clinical manifestations of the disease are reminiscent of the autoimmune diseases such as systemic sclerosis, systemic lupus erythematosus or Sjögren syndrome.[3] According to the NIH consensus global scoring system, cGvHD is categorized as mild, moderate or severe. Systemic immune-suppressive therapy is usually indicated in persons with cGvHD involving 3 or more organs or with a severity score of 2 or higher in any organ. Systemic therapy is also to be considered in persons with thrombocytopenia (platelets $<100x10^9/L$) or progressive onset during prednisone treatment.[4] cGvHD eventually leads to impaired functional performance, deteriorating quality of life, increased risk of infections and death.[21-25]

1.2.1.3 Treatment

Initial therapy for cGvHD is well established consisting of prednisone with or without a calcineurin inhibitor. However, only about 50% of persons have a durable response.[6] There are no standard recommendations for second-line treatment of cGvHD and there is no FDA approved agent. Recommendations for therapy are based on a long list of poorly standardized phase 2 trials or retrospective case analyses.[26] Diverse drugs (about 40 are described) are used, including sirolimus, tacrolimus, mycophenolate, methotrexate, extracorporeal photopheresis,

monoclonal antibodies, pentostatin, imatinib and others. Choice between drugs is based on logistics, cost, failed prior treatments, toxicity profile and subject or clinician preferences.

For many years cGvHD has been difficult to address because of the lack of standardized criteria for diagnosis, staging and response to therapy. Recently, as an effort of the NIH-sponsored Consensus Development Project, a new series of guidelines have been published addressing diagnosis and staging, histopathology, biomarkers, assessment of response to therapy, ancillary therapy, supportive care and the design of clinical trials.[22,27-31] Typically, cGvHD usually lasts 2 to 5 years, and approximately 85% of survivors are able to discontinue systemic immune suppression. Five-year survival rates for persons who develop cGvHD range from 30% to 40% for high-risk persons and persons with cGvHD resistant to steroid therapy to 70% for standard-risk cGvHD persons. Treatment goals in management of cGvHD include both alleviation of symptoms and the control and reversion of the destructive immunological process. Therapy for cGvHD is largely unsatisfactory and persons should be treated on investigational clinical protocols whenever possible.[23]

1.2.2 Thalidomide in cGvHD

Thalidomide is effective in modulating cGvHD in rodents and has been tried for the prophylaxis and treatment of cGvHD in humans.[32] Thalidomide was found to have immune modulating effects from reduced production of TNF-α, costimulation of T-cells to produce IL-2 and IFNγ, inhibition of other cytokines such as IL-1β, IL-6 and IL-12 and down-regulation of cell surface adhesion molecules involved in leukocyte migration.[26,33] It also has anti-angiogenic properties.[34] Since the report by Vogelsang et al. in 1992 presenting thalidomide as a safe and effective treatment for severe cGvHD, several other phase 2 studies in children and adults reproduced these findings in salvage treatment of cGvHD. Historically, thalidomide is the third most commonly tested drug in trials of cGvHD second-line therapy.[35] Vogelsang et al. treated 44 persons with cGvHD who were high risk at diagnosis (21) or refractory (23) to conventional treatment with thalidomide for 3 months after a complete response (CR) and for 6 months after a partial response (PR). High-risk cGvHD was defined as having 2 out of following 3 characteristics: evolving from aGvHD, lichenoid skin or mucous-membrane changes and hepatic dysfunction. Absolute survival was 64%, 78% among persons receiving salvage therapy and 48% among those with high-risk cGvHD. Complete CR was achieved in 14 persons (7 high risk, 7 salvage), PR in 12 (1 high risk, 11 salvage) and no response in 18 (13 high risk, 5 salvage). The main side effects were sedation, neuropathy and constipation.[36] In the United States, thalidomide is FDA approved for erythema nodosum leprosum and in combination with dexamethasone for newly diagnosed multiple myeloma.[37]

Six other phase 2 studies have suggested efficacy of thalidomide in high-risk or refractory cGvHD (Table 1). Most trials were small but 3 had more than 30 subjects. Complete and partial remissions (variously defined) were reported with overall response rates of 20% to 86%. Heney et al.[38] reported responses in 5 of 6 persons, best in cutaneous involvement; 2 persons developed peripheral neuropathy. In a study in children by Rovelli et al., 10 subjects responded (6 CR, 4 PR).[39] Forsyth reported a thalidomide-responsive case of pulmonary cGvHD (brochiolitis obliterans).[40] Staumont-Salle reported a response in lichenoid vulvar lesions.[41] In study by Browne et al.,[42] 38% of subjects with cGvHD responded (46% children, 25% adults). In a 1995 study by Parker et al., 20% of subjects had sustained responses, and 36% discontinued because of side effects, including sedation, constipation, neuritis, neutropenia and rash. In a phase 2 study

by Cole et al., 5 children received doses 100 to 800 mg—1 CR and 4 PRs were reported. Side effects were minimal, and there was no neuropathy.[43] Kulkarni et al. reported 13 CRs and 8 PRs in 59 subjects with cGvHD at thalidomide doses of 600 to 1200 mg/d. Two subjects had polyneuropathy, 2 had deep vein thrombosis (DVT) and 1 had thrombocytopenia. Mehta treated 6 children with cGvHD.[44] One child had a CR and one a PR. One child had a rash, eosinophilia and pancreatitis shortly after starting thalidomide, which resolved only after discontinuing thalidomide.

Two randomized trials (with approximately 50 subjects each) using thalidomide as part of the front-line therapy in cGvHD are reported.[45,46] In one open-label, add-on to steroids and cyclosporine study, comparable response rates were seen in the thalidomide and control cohorts.[45] The second study was a placebo-controlled trial using initial doses of 200 to 800 mg/d. Thalidomide had to be discontinued in 92% of persons in contrast to 65% in the placebo group due to intolerance, mostly neutropenia, sedation and neuropathy.[46] A third randomized trial of thalidomide in cGvHD was performed by Chao et al. for cGvHD prevention.[47] This study showed increased incidence of cGvHD and inferior survival in the thalidomide arm with such strategy.[47] Collectively, these data suggest efficacy of thalidomide as salvage therapy for cGvHD but not for prevention or as front-line therapy.[26]

In summary, several phase 2 trials report response rates of 20% to 83% with thalidomide doses of 100 to 1600mg/d.[26,34] Thalidomide doses higher than 200 mg/d are poorly tolerated. Phase 3 trials show, however, no benefit of thalidomide for front-line therapy and detrimental effect in cGvHD prevention. These data suggest that although thalidomide may be active at high doses in rodents, these doses cannot be reliably and safely achieved in humans. Developing pomalidomide, which has similar immune-modulating effects as thalidomide but less toxicity, is of considerable interest in cGvHD.

Table 1. Studies of Thalidomide in cGvHD

Reference	Dose (mg/day)	No. of Persons	Toxicities	Response Rate
Phase 2 salvage therapy				
Heney et al.[38] 1991	100-200	6	2 PNS not stopped	2 CR, 3 PR
Vogelsang et al.[36] 1992, steroid refractory or high-risk cGvHD	800-1600	44	4 PNS, 91% sedation during first week, 24, at least single episode of constipation	14 CR, 12 PR
Cole et al.[43] 1994	100-800	5	1 constipation	1 CR, 4PR
Parker et al.[48] 1995	400-1200	80	3 PNS, 7 somnolence, 3 constipation, 6 skin rash, 10 neutropenia	9 CR, 7 PR
Rovelli et al.[39] 1998	100-800	14	0	6 CR, 4 PR

Reference	Dose (mg/day)	No. of Persons	Toxicities	Response Rate
Browne et al.[42] 2000	200-800	37	1 constipation, 2 somnolence, 1 mild PNS, 2 severe whole-body erythema, one recovered, one died (toxic epidermal necrolysis)	1 CR, 13 PR
Kulkarni S. [49] 2003 (thalidomide in combination with CSP, prednisone and azathioprine)	600-1200	59	2 PNS, 2 DVT, 1 thrombocytopenia	13 CR, 8 PR
Phase 3 front-line therapy				
Koc et al.[46] 2000 thalidomide versus placebo, given in combination with CSP (or tacrolimus) and prednisone	200-800	52 (26 thalidomide, 26 placebo)	14 neutropenia (stopped), 11 neurologic symptoms (stopped), 17 sedation, 10 constipation	Treatment with the study drug was discontinued before resolution of cGvHD in 23 (92%) of persons
Arora et al.[45] 2001 CSP and prednisone versus CSP, prednisone, and thalidomide	200-800 (adults) 0.75-3 mg/kg (children)	54 (27 in each arm)	17 sleepiness, 1 seizures, 14 constipation, 13 PNS, 2 TTP/HUS	CR+PR similar response in both groups at 2, 6 months and 1 year; no clinical benefit when included in initial therapy
Phase 3 prevention				
Chao et al[47] 1996, randomized at day 80 after transplant	200 mg BID	59 subjects randomized, 54 evaluable (26 placebo, 28 thalidomide)		Increased incidence of cGvHD and inferior survival in thalidomide arm

Abbreviations: PNS, polyneuropathy symptoms; CR, complete response; PR, partial response; DVT, deep venous thrombosis; CSP, cyclosporine; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

1.3 POMALIDOMIDE

Pomalidomide is a novel immune-modulatory drug, a thalidomide analogue with 4,000-fold greater inhibition of TNF-α production relative to thalidomide (Celgene Corp data on file[50]). The pharmacodynamic (PD) properties of pomalidomide are of potential therapeutic benefit in the treatment of various hematologic malignancies (such as multiple myeloma and myeloproliferative neoplasm [MPN]–associated myelofibrosis and other hematologic disorders (like β-thalassemia and sickle cell disease) as well as solid cancers (prostate, thyroid and lung cancer). In addition, several features of pomalidomide suggest it may be useful in treating cGvHD, including: (1) in vitro suppression of TNF-α (human monocytes);[51] (2) increasing Th1 (mouse cancer vaccine, human CD4+ T-cells in vitro);[52,53] (3) suppression of Th2 (mouse cancer vaccine);[52] and (4) stimulation of IL-12 and sIL-2Rα (humans).[54] However, other effects of pomalidomide may have potential adverse effects in cGvHD, including: (1) increased CD45RO+ (memory) CD4 and CD8 T-cells (humans);[54] (2) decreased Tregs;[55] (3) increased Th2 (polarized human CD4+ T-cells in vitro);[53] and (4) increased B-cells (in vitro human CD19+ cells).[56] Because the precise pathogenesis of cGvHD is unknown (and may be different in different persons), it is impossible to predict the effect of therapy with pomalidomide outside of the context of a clinical trial.

1.3.1 Preclinical Studies

In a series of in vitro studies, pomalidomide exhibited several immune-modulating properties such as potent inhibition of TNF-α activity, IL-1β, IL-6, IL-12, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein, and production and inhibition of cellular cyclooxygenase-2, as well as modulation of angiogenesis. Pomalidomide also augmented the activity of natural killer (NK) cells and enhanced antibody-dependent cell-mediated cytotoxicity of targeted tumor cells in combination with therapeutic antibodies to tumor-specific surface antigens. Pomalidomide enhances T-cell stimulation by augmenting T-cell proliferation, increasing production of IL-2, IFN-γ and RANTES, and decreasing IL-10 production. Furthermore, pomalidomide is a potent inhibitor of the proliferation of multiple myeloma cell lines in vitro and has been shown to be active in subjects with relapsed or refractory myeloma.[54,57] Based on its numerous mechanisms of carcinoma growth inhibition, pomalidomide is being tested as part of induction chemotherapy regimens and as post-induction maintenance therapy for solid cancers.

More information emerged recently about the specific mode of pomalidomide action as cereblon (*CRBN*), the primary target for thalidomide teratogenicity[58], is now identified also as an essential target for pomalidomide anti-myeloma activity.[59] The immediate result of this binding is interferon regulatory factor 4 (IRF4) down-regulation, which is also essential for Th-17 cell development.[60,61]

1.3.2 Animal Models

Oral pomalidomide is rapidly absorbed in rats and monkeys and the bioavailability is dose dependent, at high doses 100mg/kg, the bioavailability was low (15%) however at 2mg/kg the bioavailability was 100%. Following intravenous (IV) administration to rats and monkeys, pomalidomide exhibited low clearance (240 to 286 mL/h/kg), a moderate volume of distribution (2.2 to 2.5 L/kg), and a moderately long terminal half-life (approximately 6 hours). Renal excretion of metabolites was the predominant route of clearance in animal models. The toxicity

of pomalidomide after oral and IV dosing was studied in rats and mice. There were no deaths and no significant clinical observations in rodents given a single dose of pomalidomide at 2000 mg/kg orally or up to 50 mg/kg IV. No treatment-related macroscopic changes were observed. In rats administered a single dose of 10, 25 and 50 mg/kg pomalidomide by IV injection, the high dose produced piloerection, hunching, and tachypnea. Palpebral closure was observed at doses of 25 and 50 mg/kg, and hyperpnea at 50 mg/kg. The severity and persistence of clinical observations increased with increased dose. Pomalidomide at oral doses of 100, 500 or 1500 mg/kg was well tolerated when given once daily to male and female rats for 90 consecutive days. Therefore, the no-observable-adverse-effect level (NOAEL) under the conditions of this study was 1500 mg/kg.

A 13-week study evaluated the toxicity and toxicokinetics of pomalidomide in male and female cynomolgus monkeys after oral doses of 0.05, 0.2, 2 or 10 mg/kg. Lesions in the bone marrow, spleen, and thymus were observed in animals dosed at 2 and 10 mg/kg. Based on the results from this study, the NOAEL was 0.2 mg/kg/day; the maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC) values at this dosage were approximately150 ng/mL and 600 ngh/mL, respectively. Since the monkey was identified as the most sensitive species in the toxicology program, the NOAEL of 0.2 mg/kg/day was used to calculate the human equivalent dose of 0.06 mg/kg or 3.8 mg for a 60 kg person. External and cardiac malformations were observed in fetuses of pregnant rabbits that were administered pomalidomide orally at 10, 100 and 250 mg/kg/day. A relationship was noted between increasing pomalidomide dose and the number of fetuses affected, as well as the frequency of occurrence of each type of malformation. Based on these data, it was concluded that pomalidomide causes fetal malformations in rabbits. A nonclinical safety PD study demonstrated no major safety concerns with cardiac and respiratory functions in dogs, rats or monkeys. In rats and monkeys pomalidomide administrated orally was absorbed fairly rapidly (T_{max} of 2 to 4 hours) and had low oral bioavailability (13%-15%). Renal excretion was the predominant route of clearance in animal models.

In the mouse model of bleomycin-induced skin fibrosis, pomalidomide exerted potent anti-fibrotic effects and not only prevented progression of experimental fibrosis, but also induced regression of established fibrosis. In this model, pomalidomide reduced dermal thickening and reduced the numbers of myofibroblasts in the skin, whether it was administered prophylactically or therapeutically. These results show that pomalidomide exerts potent anti-fibrotic effects and not only prevents the progression, but also induces a regression of established fibrosis in a nonclinical model of skin fibrosis (Celgene, unpublished).

In multiple myeloma, pomalidomide induces growth arrest and/or apoptosis of multiple myeloma cells (via caspase-8 death receptor pathway), and it also reduces stromal cell expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which decreases angiogenesis. [62] One characteristic of immune-modulatory drugs is their potency to act as a co-stimulus of T-cell receptor ligation, leading to increased production of IL-2 and INF-γ, indicative of a Th1 phenotype.[63] Pomalidomide promotes T-cell differentiation via the augmentation of T-bet, which leads to upregulation of INF-γ.[63] It also increases antibody-dependent cell cytotoxicity.

1.3.3 Experience in Humans

Pomalidomide is active in multiple myeloma and MPN-associated myelofibrosis. It has been also used to treat cGvHD. Given at doses up to 3 mg/day is usually well tolerated and main toxicities are neutropenia and thrombocytopenia, there have been no drug-related deaths in clinical trials with pomalidomide (summarized in Table 2).

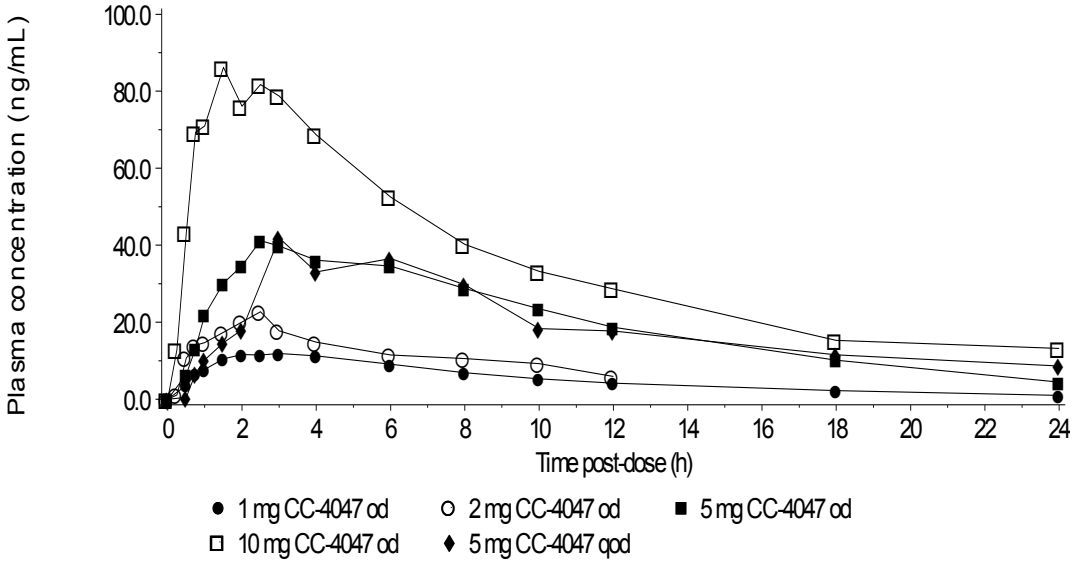
1.3.3.1 Pharmacokinetics and Product Metabolism in Humans

A phase-1, single-center, single-blind, placebo-controlled, ascending single oral dose study (CC-4047 1398/132) was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of pomalidomide in 30 healthy male subjects, aged 19 to 55 years. Pomalidomide was administered orally in capsule form at 5 dose levels comprised of 1, 5, 10, 25, and 50 mg, and corresponding to 0.01, 0.07, 0.13, 0.30, and 0.59 mg/kg, respectively, when adjusted for group mean body weight. At each dose level, 4 subjects received pomalidomide and 2 subjects received placebo in a fasted state. A total of 20 subjects each received a single oral dose of pomalidomide in doses ranging from 1 mg to 50 mg, and 10 received placebo. Following each dose level of pomalidomide, the absorption of pomalidomide was moderately rapid. The maximum plasma concentration (C_{max}) occurred at a median t_{max} of 2.5 to 6 hours postdose. The systemic exposure of pomalidomide as determined from the area under the plasma concentration-time curve [$AUC_{(0\text{-}tz)}$ and $AUC_{(0\text{-}\infty)}$] increased in an approximately dose-proportional manner, whereas C_{max} increased in a subproportional manner. After reaching C_{max}, plasma concentrations of pomalidomide declined in an apparent biphasic manner. The geometric mean terminal elimination half-life ($t_{1/2}$) ranged from 8.2 to 10.8 hours, with no apparent dose-related trend. Less than 3% of the administered dose was excreted in urine as unchanged pomalidomide across all dose levels.

A phase-1b, single-center, ascending dose, open-label study (CDC-407-00-001) was conducted to identify the MTD and evaluate the safety and efficacy of pomalidomide in male and female subjects with relapsed or refractory Multiple Myeloma (MM). Pomalidomide was administered orally in capsule form at doses of 1, 2, 5, and 10 mg in either once daily dosing (Cohort 1) or alternate day dosing (Cohort 2) for 4 weeks. The study design did not allow for a precise calculation of subject numbers, as the number of subjects per dose group was dependent on the frequency of DLT. Subjects were enrolled in groups of 3 per dose group beginning with the 1-mg dose group. If no DLT were experienced (in one dose group) at a given dose level, the subsequent group of 3 subjects were to receive the next highest dose. If 1 of the 3 subjects in a dose group experienced a DLT, that cohort would then be expanded to 6 subjects. If 2 or more subjects in a cohort of up to 6 subjects experienced a DLT, no additional escalation of dose would occur. Escalations would occur until an MTD was established or the maximum dose of 10 mg/day was reached. A DLT was defined as a Grade 3 or higher non-hematologic toxicity or a Grade 4 or higher hematologic toxicity using the NCI CTC. A total of 45 subjects were enrolled in the study; 24 subjects in Cohort 1 and 21 subjects in Cohort 2. Blood samples for the analysis of pomalidomide were collected from 28 subjects and included in the pharmacokinetic analysis. Dose levels of pomalidomide evaluated in the pharmacokinetic assessment were 1, 2, 5, and 10 mg once daily and 5 mg on alternate days. Blood and urine samples for analysis of plasma and urinary pomalidomide concentrations were collected for up to 24 hours after dosing on Day 1 and Week 4 (Day 29). Plasma concentrations (Geometric means and coefficient of

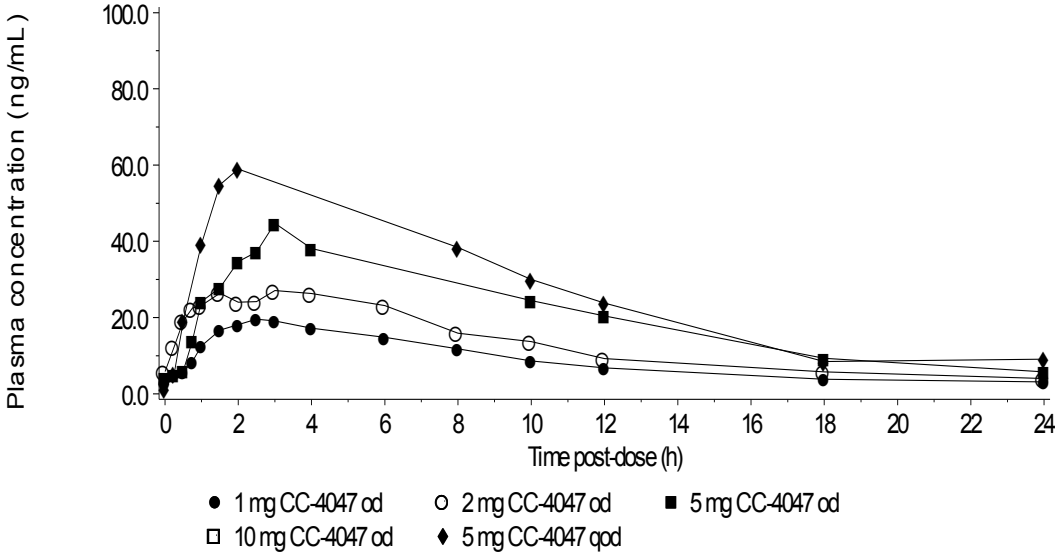
variation percent [CV%]) of pomalidomide in subjects with MM on Day 1 and Week 4 are summarized in Figure 1 and Figure 2.

Figure 1: Plasma Concentrations of Pomalidomide on Day 1



OD = once daily; QOD = every other day.

Figure 2: Plasma Concentrations of Pomalidomide on Week 4



OD = once daily; QOD = every other day.

Following administration of pomalidomide at dose levels of 1, 2, 5, and 10 mg once daily and 5 mg every other day to subjects with MM, absorption of pomalidomide was steady with median t_{max} ranging from 1.5 to 4.0 hours postdose on Day 1 and Week 4. The mean $t_{1/2}$ of pomalidomide was similar across dose levels and dosing days being approximately 7 to 8 hours.

At the 1 and 2 mg daily dose levels, there was slightly greater accumulation of pomalidomide in plasma upon multiple dosing than predicted. However, at the 5 mg daily and 5 mg alternate day dose levels, there was little or no accumulation of pomalidomide upon multiple dosing.

There was a less than dose proportional increase in $AUC_{(0-\infty)}$ and C_{max} for pomalidomide over the 1 to 10 mg dose range on Day 1, with a more pronounced sub-proportional increase in both parameters on Week 4 over the 1 to 5 mg dose range.

The fraction of the dose excreted in the urine as unchanged drug was low for all dosing regimens, with a maximum of 4.5% being eliminated up to 24 hours after dosing on Day 1 and Week 4 for individual subjects.

1.3.3.2 Clinical studies with Pomalidomide

In a phase 1 single-center, single-blind, placebo-controlled, ascending single-dose study, pharmacokinetics (PK), PD and safety of pomalidomide were studied in 30 healthy male subjects. The results demonstrated that pomalidomide administered at a dose of 1 to 50 mg has an acceptable safety profile. Adverse events (AEs) reported in the study were mild or moderate in nature and no clinically significant changes in any laboratory or other parameters, except a dose-related decrease in the CD4+ cell count, were observed.

A phase 1b study was conducted to identify the maximum tolerated dose (MTD) and evaluate safety and efficacy of pomalidomide in persons with relapsed or refractory multiple myeloma. A total of 24 persons were treated with the dose-escalating regimen (1, 2, 5 and 10 mg). The MTD was 2 mg. Pomalidomide was well tolerated with no serious nonhematological AEs and excellent disease responses. Fifty-eight percent of persons developed grade 3/4 neutropenia and 16% of persons developed DVT. [64] In this study, the cytokines were measured and it was noticed that the serum IL-12 and sIL-2 levels increased during the first 4 weeks of treatment. IL-12 is derived from monocytes and macrophages and has a key role in amplifying a Th1-type response.[65] No significant changes and no correlation was found between IL-6, TNF-α, IL-10, VEGF and bFGF levels and paraprotein response.

A standard dose escalation phase 1 study was conducted to determine the MTD of pomalidomide at 1 mg, 2 mg, 5 mg, and 10 mg on alternate days in persons with relapsed myeloma. Patients were evaluated prior to study enrolment and weekly for the first month and monthly thereafter. The overall response rate (>50% reduction in paraprotein) to pomalidomide monotherapy was 50%. Hematological monitoring over 4 weeks showed significant decline in hemoglobin, white blood cells, and neutrophils. Platelets decreased but without statistical significance. Significant decrease was noticed in the B-cell percentage (P=0.002) and absolute B-cell number. The CD3+ percentage and CD8+ percentage increased (P=0.003, P=0.007). The CD4+ percentage and absolute as well as NK cell percentage were increased but without statistical significance. There was a significant negative association between B-cell percentage or absolute B-cell count at 4 weeks and maximal percentage change in paraprotein (P=0.05, P=0.03).

Tefferi et al. published a phase 2 randomized, multicenter, double-blind study of pomalidomide in MPN-associated myelofibrosis. Four arms were studied pomalidomide (2 mg) plus placebo,

pomalidomide (2 mg) plus prednisone, pomalidomide (0.5 mg) plus placebo and pomalidomide (0.5 mg) plus prednisone. Pomalidomide was well tolerated. Anemia response rate was up to 40%. There was relatively low incidence of grade ≥3 neutropenia and thrombocytopenia. How pomalidomide works in MPN-associated myelofibrosis is unclear, but it is known that TNF-α directly inhibits erythropoiesis in vitro.[66] In this study it was also described that overall bone marrow cellularity, degree of fibrosis, or cytogenetic findings did not change (bone marrow examination was done in 4 responders who completed 1 year treatment with pomalidomide with or without prednisone.

A multicenter, randomized, phase 2 study of pomalidomide in combination with low-dose dexamethasone was conducted in patients with relapsed/refractory myeloma who received prior therapy (lenalidomide or bortezomib). Pomalidomide 2 mg po daily was given on days 1 through 28 of a 28-day cycle. Dexamethasone 40 mg daily was given on days 1, 8, 15 and 22 of each cycle. Thirty-eight patients achieved objective response (63%), including CR in 5%, very good PR in 28% and PR in 30%. Responses were seen in 40% of lenalidomide-refractory persons, 37% thalidomide-refractory and 60% of bortezomib-refractory persons. Toxicity was primary myelosuppression. Grade 3 or 4 hematologic toxicity consisted of anemia (5%), thrombocytopenia (3%) and neutropenia (32%). Among those that developed grade 3/4 neutropenia, all first experienced the neutropenia in cycle 1-3; no new patients experienced grade 3/4 neutropenia in cycle 4 or later. One patient experienced thromboembolic event. The most common non-hematologic grade 3 or 4 toxicities consisted of fatigue (17%) and pneumonia (8%); less than 5% of patients experienced neuropathy, diarrhea, constipation or hyperglycemia. One patient (1.6%) had a thromboembolic event of DVT.

In a phase 1/2 study in MPN-associated myelofibrosis with 19 patients, 3 mg was determined to be the MTD, but no efficacy was observed at that dose. Two of three patients in the 3.5 mg cohort had dose-limiting myelosuppression. Overall, 7 subjects had an anemia response and 2 a spleen response.

In another trial of pomalidomide in MPN-associated myelofibrosis, low-dose pomalidomide (0.5 mg/day) was given to 58 persons. Anemia response was documented only in persons with JAK2V617F (24 vs 0%; P=0.03). Nine of the 10 anemia responders became red blood cell–transfusion independent. Fourteen of 24 persons with platelets ≤100x10e9 /L had a greater than 50% increase in platelets. Grade 3 or 4 thrombocytopenia/neutropenia occurred rarely. This study established low-dose pomalidomide as effective and safe in MPN-associated myelofibrosis with anemia.

1.3.3.1 Pomalidomide in cGvHD

Pusic et al. reported results of a phase 2 study of pomalidomide in patients with cGvHD not controlled by corticosteroids.[67] Eight subjects received 3 mg/day with dose reductions to 2 mg, 1 mg and 0.5 mg. Seven subjects required dose reduction because of muscle cramps, tremor and fatigue. Five subjects discontinued therapy for worsening of cGvHD of the skin and mouth (N=1), pain (N=1) and no response (N=3). No bone marrow suppression, somnolence, constipation or DVT were observed. Three persons reached the primary evaluation endpoint at 6 months at the 2 mg dose (N=2) or 1 mg dose (N=1). The 3 patients had global PRs per NIH criteria (skin erythema, GI) and <PR ongoing improvements in the skin, mouth and eyes. This study established feasibility of giving pomalidomide to humans with cGvHD and the absence of serious side effects at doses less than 2 mg/day.

Table 2. Clinical Studies of Pomalidomide

Reference	Setting	Study Design	Study Duration	Dose	N	MTD	Toxicities	Response Rate
Phase 1								
Celgene, not published	Healthy volunteers	Single-blind, placebo-controlled, ascending single dose		1, 5, 10, 25, 50 mg	30, 10 received placebo	N/A	Mild or moderate AEs; no clinically significant changes in any laboratory parameter tested	N/A
Streetly et al.,2008[64]	Relapsed MM	Standard dose escalation	4 weeks	1, 2, 5, 10 mg	20	5 mg	10 mg, grade 4 neutropenia in 3/3 pts, DVT 0%	10% CR and >50% reduction in paraprotein in 50%
Schey et al., 2004[65]	Relapsed or refractory MM	Dose escalating regimen	4 weeks	1, 2, 5, 10 mg	24	2 mg	Grade 3/4 neutropenia in 58% pts and DVT in 16%	17% CR, >25% reduction in paraprotein in 67% , >50% reduction in paraprotein in 54%
Phase 2								
Tefferi et al. 2009[37]	Anemia associated with myelofibrosis	Randomized, double-blind, multicenter	Up to 12 28-day treatment cycles	4 arms (2 mg+ placebo, 2 mg + prednisone, 0.5 mg + prednisone, and prednisone	84	2 mg	Relatively low incidence of grade ≥3 neutropenia and thrombo-cytopenia	Response in anemia 20 pts (40%) 23%, 2 mg/d + placebo; 16%, 2 mg/d + prednisone; 36%, 0.5 mg/d + prednisone; 19%, prednisone +

				+ placebo				placebo
Mesa et al., 2009 [68]	Myelofibrosis	Phase 1/2, multicenter dose escalation	28 days	2.5, 3.0 and 3.5 mg/day; no efficacy at 3 mg, dose reduction to **0.5 mg**	19	3 mg	DLT myelosuppre-ssion in 2/3 pts in 3.5 mg cohort	7 pts anemia response, 2 spleen response
Lacy et al., 2009 [69]	Relapsed MM	Multicenter	2 mg/d on days 1-28 of a 28-day cycle, dexame-thasone 40 mg on days 1, 8, 15, 22	2mg/day	60		Primarily myelosuppression. Grade 3 or 4 hemato-logic toxicity consisted of anemia (5%), thrombo-cytopenia (3%) and neutropenia (32%)	Objective response in 63%, including CR in 5%, very good PR in 28% and PR in 30%
Begna et al., 2011[70]	Myelofibrosis (JAK2V617F positive)	Single-center	28-day cycles: 84% pts had ≥3 cycles	0.5 mg/day, after 6 cycles 2 mg/day	58	2 mg	No AE reason for stopping therapy. 1 pt neuropathy, 1 pt grade3/4 thrombo-cytopenia	10 (17%) anemia response, 20% anemia RR in pts who received ≥3 cycles
Pusic et al., 2010[67]	cGvHD	Multicenter, response evaluated every 3 months		3 mg/day with dose reductions to 2, 1 and 0.5 mg/day	8	3 mg	Muscle cramps, tremor and fatigue	2 CRs, 1 PR (3 pts reached 6 months)

1.4 STUDY DESIGN AND RATIONALE

Better therapies for cGvHD are needed. In about 50% of persons with cGvHD, the disease does not respond to corticosteroids, and there is no standard second-line therapy or FDA-approved drug for cGvHD. Thalidomide is an immune-modulating drug effective in a rodent model of cGvHD and in humans for salvage therapy after failure of steroids, but at doses expected to be effective it is associated with troublesome side effects including somnolence, neuropathy and constipation, which precluded wider use in this population. Pomalidomide is a new immune-modulating drug that is more potent than thalidomide and has been shown in early trials in cancer and cGvHD to be without the toxicities that limited the use of thalidomide. Several biological features of pomalidomide suggest that this drug may be useful in treating cGvHD. Since the precise pathogenesis of cGvHD is unknown, the most compelling evidence for testing pomalidomide in a clinical trial is the encouraging efficacy data with thalidomide. Preliminary studies of pomalidomide in persons with cGvHD suggest absence of typical thalidomide-related side effects or significant myelosuppression and a preliminary suggestion of efficacy if doses of less than 3 mg/day could be given for at least 6 months (the typical primary response evaluation time point in cGvHD trials).

The use of the NIH Consensus Diagnosis, Staging Criteria now provides an updated, standardized assessment of persons with cGvHD for inclusion in clinical trials.[71,72] Although NIH Consensus Response Criteria are not yet validated in large clinical trials there are preliminary data on validity and reproducibility that provide guidance for further use and testing.[73]

At the intramural NCI there is a well-established clinical research infrastructure, the "NIH Chronic GVHD Study Group," that is uniquely qualified to conduct drug development studies and cGvHD assessments in a multi-disciplinary specialty setting. This environment is also uniquely conducive for further studies of cGvHD biology and in vivo pomalidomide effects by using the ETIB immunology pre-clinical core and the established cGvHD murine models expertise. The proposed study is not only expected to address a specific clinical therapeutic question related to pomalidomide in cGvHD but also allows establishment of experience with this important group of agents in general in patients after allogeneic hematopoietic stem cell transplantation.

The proposed study is a randomized phase 2 trial with the single stage selection design Patients will receive either a constant low dose of pomalidomide (0.5 mg/day) for six months or a strategy of increasing dose of pomalidomide from 0.5 mg/d up through each individual patients' maximum tolerated dose, with escalations by 0.5 mg/d every 2 weeks to a maximum of 2.0 mg/d. To protect patient safety, an early stopping rule will be implemented as outlined in section **8**. With two arms, each of which has a maximal accrual of 16 patients, up to 32 evaluable patients will be randomized. Response assessments will occur every 3 months with primary efficacy endpoint evaluated at 6 months. Patients with responding disease will continue therapy for another 6 months.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Moderate or severe cGvHD diagnosed and staged per NIH criteria (Filipovich et al 2005)[22], Appendix C , Appendix D, Appendix E and Appendix F..

2.1.1.2 ≥18-75 years of age, because no dosing or adverse event data are currently available on the use of pomalidomide in persons <18 years of age

2.1.1.3 Has cGvHD that did not respond to high-dose corticosteroids (average 0.5 mg/kg/d prednisone for ≥8 weeks) or second-line systemic therapy

2.1.1.4 If taking systemic therapy for cGvHD at the time of enrollment, must be on a stable or tapering schedule in the preceding 4 weeks (extracorporeal photopheresis has to be stopped at least by 4 weeks before enrollment)

2.1.1.5 Karnofsky performance score ≥60% (Appendix A)

2.1.1.6 Life expectancy >3 months

2.1.1.7 Stable primary malignancy for previous 3 months

2.1.1.8 Agree to adhere to methods of contraception and other fertility control measures as prescribed by the protocol

- Agents of this class are known to be teratogenic, women of child-bearing potential and men must agree to use effective forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Female Subjects
  - Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting pomalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking pomalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy. All patients must be counseled every 28 days about pregnancy precautions and risks of fetal exposure through the POMALYST REMS™ program. See Appendix M: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
- Male Subjects
  - Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days

[†] A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

following discontinuation of study drug even if he has undergone a successful vasectomy
  - Will be warned that sharing study drug is prohibited and will be counseled about pregnancy precautions and potential risks of fetal exposure
  - Must agree to abstain from donating blood, semen, or sperm during study participation and for at least 28 days after discontinuation of study drug.
  - Must agree that if a pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued.

- Patients must agree to not share study drug with anyone during participation in the study.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.10 All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.

2.1.2 Exclusion Criteria

2.1.2.1 Acute GvHD, classic (≤day 100) or late-onset (>day 100) Appendix D

2.1.2.2 Systemic immune suppression or systemic therapy for cGvHD started within preceding 4 weeks including extracorporeal photopheresis

2.1.2.3 Hypersensitivity to thalidomide, lenalidomide or pomalidomide

2.1.2.4 Any serious medical condition which places the subject at an unacceptable risk if he or she were to participate in the study or confounds the ability to interpret data from the study, including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.5 Neutrophil $<1.0x10^9$/L, platelets $<75x10^9$/L, estimated creatinine clearance <50 mL/min/1.73m^2 (Cockroft-Gault formula) total bilirubin >3 mg/dL, transaminase >3xUNL

2.1.2.6 Uncontrolled infection

2.1.2.7 Active HIV-1, HBV and/or HCV infection

2.1.2.8 Uncontrolled arrhythmias or symptomatic heart disease or LVEF <45%

2.1.2.9 Other cancer except that for which the transplant was done <2 years before study entry, except non-melanoma skin cancer or carcinoma in situ of the uterine cervix or breast

2.1.2.10 Taking other investigational drugs

2.1.2.11 NIH lung score 3 (Appendix E)

2.1.2.12 Pregnant women are excluded from this study because pomalidomide has potential for teratogenic effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pomalidomide, breastfeeding

must be discontinued while the mother is taking study drug and for at least 28 days after discontinuation of study drug. These potential risks may also apply to other agents used in this study.

2.2 REQUIRED TESTING AND COUNSELING FOR FCBP AND PARTNERS OF FCBP

2.2.1 During study participation and for 28 days following discontinuation of study drug:

- Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
- Pregnancy tests must occur 10 – 14 days and again within 24 hours prior to initiation of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14 days while on therapy (including breaks in therapy), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (see Appendix M: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
- All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done every 28 days and at drug discontinuation through the POMALYST REMS™ program. See Appendix M: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

2.3 SCREENING EVALUATION

Screening procedures may be performed on a CCR screening protocol, most commonly on 04-C-0281 "Natural History of Chronic GVHD." All studies must be completed within 8 weeks prior to enrollment:

- History and physical exam, Karnofsky performance score
- Documentation of cGvHD diagnosis, NIH organ and global severity stage
- CBC, platelets, differential, PT/PTT, serum chemistries (including sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST [SGOT], ALT [SGPT], lactate dehydrogenase [LDH], and uric acid), urinalysis, urine pregnancy testing, TSH
- Infectious serology markers (HIV-1, HBV, HCV)
- Determination of estimated creatinine clearance
- Pulmonary function testing, CT of the chest (BOS sequence), cardiac ECHO, ECG
- Social work screening consult

For baseline evaluations, please see Section **2.6**.

2.4 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.5 RANDOMIZATION PROCEDURES

Randomization will be done at the time of enrollment by the Central Registration Office, which will perform the randomization using randomization assignments determined by the study statistician. Subjects will be randomized to one of two treatment arms: low dose (0.5 mg/d) and high dose (0.5, escalating every two weeks to 1.0. 1.5 or 2.0 mg/d) pomalidomide. If one of the arms closes due to futility, toxicity or completion, enrollment will continue to the remaining arm.

2.6 BASELINE EVALUATION

Following studies will be performed at the baseline before/after the enrollment and within four weeks prior to starting taking the study drug unless otherwise indicated below:

- History and physical exam, Karnofsky performance score
- CBC, platelets, differential, PT/PTT, serum chemistries (including sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST [SGOT], ALT [SGPT], lactate dehydrogenase [LDH], and uric acid), CRP, total complement and C3 and C4, urine pregnancy testing (once within 10-14 days prior to the start of study drug and again within 24 hours prior to the start of study drug), immunoglobulin levels, TBNK, blood CMV PCR, drug levels if pertinent (e.g., cyclosporine, tacrolimus, sirolimus)
- MRI of the involved extremity if clinically indicated (acceptable if done within 8 weeks)
- Documentation of cGvHD per NIH criteria (diagnostic, distinct, other and common manifestations), NIH organ and global stage, baseline assessments (form A and form B) per NIH response criteria, date of cGvHD diagnosis, prior and current treatments, prednisone or other steroids oral dose, and other patient, donor and transplant characteristics per Appendix Q.
- Specialty evaluations of cGvHD: dermatology, ophthalmology, dental, rehabilitation and occupational therapy, gynecology if applicable (can be done up to two weeks after starting study drug, except for dermatology and dental evaluations which must be done prior to starting study drug)

- Diagnostic and research biopsies of the skin and mouth (all persons), and other organs (only if clinically indicated)
- ECG
- Research laboratory (blood, saliva, urine)
- Study drug dispensation
- Subject diary review
- Documentation of concurrent medications

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

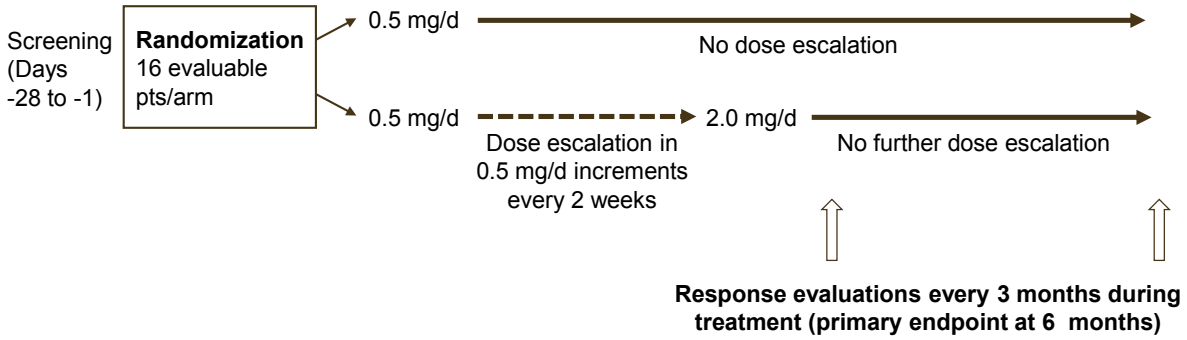
The study is a randomized phase 2 trial with the single stage selection design. It is known from prior trials that the maximum tolerated dose of pomalidomide is about 3 mg/d in persons with bone marrow disorders receiving prior therapies for cancer, in cGvHD doses <3mg/d have been well tolerated. This study will explore clinical toxicity of gradual escalation of pomalidomide doses <3 mg/d in subjects with cGvHD. Patients will receive either a constant low dose of pomalidomide (0.5 mg/day) for six months or a strategy of increasing dose of pomalidomide from 0.5 mg/d up through each individual patients' maximum tolerated dose, with escalations by 0.5 mg/d every 2 weeks to a maximum of 2.0 mg/d. In each of the two arms, the trial will use a single stage design. As an early stopping rule for futility as outlined in section **8**, if after 7 patients have enrolled on either arm, 0 have responded, then no further patients will be accrued to that arm as soon as this can be determined. To protect patient safety, an early stopping rule will be implemented. With two arms, each of which has a maximal accrual of 16 patients, up to 32 evaluable patients will be randomized. Safety assessments and pregnancy testing for FCBP will be performed at scheduled intervals as described in the Study Calendar.

Response will be assessed every 3 months while taking pomalidomide following the criteria in Section **6.2**. The primary efficacy endpoint will be evaluated at 6 months. Efficacy outcome is defined as clinical response (CR or PR) in subjects who enter the study with stable cGvHD or stable disease for ≥3 mo for subjects with progressive cGvHD at study-entry. (Stability will be assessed by the clinician and by the clinical exam at the screening evaluation based on the clinician estimate of the disease trajectory during the 3 months pre-randomization). Subjects who meet the response criteria at 6 months will continue therapy for another 6 months. If in the subject's best interest, efforts will be made to provide access to study drug on compassionate basis beyond the 12-month study endpoint.

Patients who discontinue therapy for any reason will be followed for up to 24 months after starting pomalidomide as described in Section **6.1.3.**

Concurrent topical and ancillary treatments for cGvHD are allowed per standards of care and will be recorded (see Section **4**).[27] Other systemic immune suppression must stay stable or be tapered (systemic immunosuppression taper should be attempted no earlier than after 4-6 weeks on study), throughout the treatment with pomalidomide (with up to 2 steroid pulses allowed for disease stabilization per Section **4.1**).

Study Schema



3.1.1 Dose-Limiting Toxicity

DLT will be defined as any grade ≥3 adverse event which is thought to be probably or definitively related to the investigational drug administration (notable exceptions where grades 2 or lower can be considered as DLTs are indicated in Table 4 below in Section **3.3**). In addition, any persons who are unable to tolerate the dose to which they are assigned will be counted as a DLT at the maximum dose explored for that patient. The time frame for evaluation in which toxicity will count towards a DLT will be up to 28 days after therapy received at a given dose level. In addition, a grade ≥ 3 AE will not be considered as DLT if the adverse event is attributed to a GVHD flare and responds to steroid pulse therapy as outlined in section **4.1**. Whether treated on either arm, if there are 2 patients in the first 6 who experience a DLT from a given dose level, then no further patients will be treated at that dose level on the trial, regardless of arm. Furthermore, when more than 6 patients have received a given dose level, if at any time 33% or more patients experience a DLT when treated at that dose level, then no further patients will be treated at that dose level. Data from all subjects who receive ≥1 dose of pomalidomide will be include in the safety analysis.

3.1.2 Dose Escalation

All subjects, independently of the randomization arm, will start pomalidomide at 0.5 mg/d. Those randomized to the high-dose arm will escalate to the target dose level by increasing the pomalidomide dose in 0.5 mg increments (**Table 3**) every 2 weeks to the next level. If the escalation is not tolerated, the patient will be treated on the next lower dose level. MTD designation will be given to the highest dose in which no more than 1 DLT occurred per cohort.

Table 3. Pomalidomide Dose Escalation Steps (high-dose arm)

Dose Level	Dose
Starting Dose (level 1)	**0.5 mg daily on Days 1-14**
Dose Level 2	1.0 mg daily on Days 15-28
Dose Level 3	1.5 mg daily on Days 29-42
Dose Level 4	2.0 mg daily on Days 43-56

3.2 DRUG ADMINISTRATION

Pomalidomide will be given as 0.5 mg, 1.0 mg, or 2.0 mg capsules to be taken orally once a day on days 1–28 of a 28-day cycle. Each daily dose of pomalidomide should be taken at approximately the same time of day. Patients will be asked to complete a medication diary (Appendix P).

Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

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

Patients are instructed to fast (water or clear fluids only) for at least 2 hours prior to taking a dose to at least 1 hour post dosing. Pomalidomide should not be swallowed concurrently with other allowed medications while on-study.

3.2.1 Drug Dispensing

Pomalidomide (POMALYST®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ program. Per the standard POMALYST REMS™ program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

Drug will be shipped on a per patient basis by the contract pharmacy to the NIH pharmacy for IND studies. Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ program.

Only enough pomalidomide capsules for 1 cycle of therapy may be provided to the patient each cycle.

Patients will be asked to maintain a dairy and bring to the next appointment all remaining capsules.

3.3 DOSE MODIFICATIONS

Patients requiring dose reduction will be reassigned to one of the lower dose cohorts being evaluated: 0.5, 1.0 or 1.5 mg. Patients may be dose reduced to the lowest possible dose, i.e. 0.5 mg. For any dose reductions or if study drug needs to be held greater than 35 days, the Principal Investigator (PI) or Lead Associate Investigator (LAI) must be contacted. Once a dose has been reduced, it cannot be re-escalated. At the discretion of the PI, the use of granulocyte colony-stimulating factor (G-CSF) will be permitted to manage neutropenic fever or a Grade 4

neutropenia. Given the potentially long treatments delays, patients must have received 75% of the doses prescribed to be considered evaluable for the primary study endpoint.

Table 4. Dose Modifications

Common Terminology Criteria (CTCAE) Version 4.0	**Adverse Event**	**Dose Change for Pomalidomide**
Allergy/ Immunology	Allergic reaction/ hypersensitivity (including drug fever) - Grade 2	Hold study drug until resolved to < Grade 1; Decrease dose by 1 dose level
Allergy/Immunology	Allergic reaction/ hypersensitivity (including drug fever) - Grade 3 or 4	Discontinue Study Drug
Blood/Bone Marrow	Neutropenia (ANC) - Grade 3 with fever or Grade 4	Hold study drug until < Grade 2; Decrease dose by 1 dose level
Blood/Bone Marrow	Thrombocytopenia - Grade 3 or 4	Hold study drug until <Grade 2; Decrease dose by 1 dose level
Blood/Bone Marrow	Anemia - Grade 3 or 4	Hold study drug and treat anemia as needed until Hgb within 0.5 g/dL of lower limit of normal; Decrease dose by 1 dose level
Cardiac Arrhythmia	Grade 2	Hold study drug until resolved to < Grade 1; Decrease dose by 1 dose level
Cardiac Arrhythmia	Grade 3 or 4	Discontinue study drug
Prolonged QTs Interval	Grade 3 (>0.50 second)	Hold study drug; decrease dose by 1 dose level and restart when resolved to < Grade 2
Prolonged QTs Interval	Grade 4 (>0.50 second, life threatening symptoms)	Discontinue study drug
Vascular	Thrombosis/embolism - Grade 2, 3 or 4	Discontinue study drug

Common Terminology Criteria (CTCAE) Version 4.0	**Adverse Event**	**Dose Change for Pomalidomide**
Dermatology/ Skin	Rash non-desquamation - Grade 3	Hold study drug until resolved to < Grade 1. Decrease dose by 1 dose level
Dermatology/ Skin	Rash non-desquamation - Grade 4	Discontinue study drug
Dermatology/ Skin	Rash / desquamation - Grade 3, 4 Rash / desquamation - Grade 2	Discontinue study drug The dose may be modified or discontinued at the investigators discretion.
Dermatology/ Skin	Rash Erythema multiforme	Discontinue study drug
Endocrine	Elevated or Reduced Thyroid Function Test results without symptoms of hyper- or hypo-thyroidism	Confirm test results and if significant, refer for therapy; Do not alter study drug regimen
Endocrine	Elevated or Reduced Thyroid Function Test results with symptoms of hyper- or hypo-thyroidism	Hold study drug; Evaluate etiology and refer for appropriate therapy; Restart at the prior dose once symptoms have resolved and thyroid function has been stabilized with medical and/or surgical intervention
Neurology	Neuropathy cranial/motor/ sensory - Grade 2	Hold study drug; Restart at same or 1 dose level lower once event has resolved to < Grade 1
Neurology	Neuropathy cranial/motor/ sensory Grade 3 or recurrence of Grade 2	Hold study drug until resolved to < Grade 1; Decrease dose by 1 dose level
Neurology	Neuropathy cranial/motor/ sensory - Grade 4	Discontinue study drug

Common Terminology Criteria (CTCAE) Version 4.0	**Adverse Event**	**Dose Change for Pomalidomide**
Other pomalidomide related toxicity	Grade 3 or Grade 4	Hold pomalidomide therapy; Decrease dose by 1 dose level and restart when resolved to < Grade 2

3.4 QUESTIONNAIRES

Patient self-report questionnaires administered in this study are part of the standard NIH chronic consensus recommended criteria for the evaluation of cGvHD in clinical trials.[29] These standardized assessments are designed to evaluate patient quality of life (SF-36, FACT-BMT), functional performance (HAP) and symptoms (Lee symptom scale, symptom intensity scale). The purpose of these evaluations is to assess the potential benefit of the administered therapy as compared to the baseline. These forms have been extensively used, published and validated. These forms are also standard part of many NCI CCR cGvHD protocols (Appendix G). In a recent study median time for persons to complete these forms was 15 minutes (range 8-22 minutes).[73]

3.5 STUDY CALENDAR

Assessments	**Screening**	**BL**						**3 mos**		**6 mos**		**9 mos**		
		BL/ C1 D1	**C1 D15 (+/-2 days)**	**C2 D1 (+/-2 days)**	**C2 D15 (+/-2 days)**	**C3 D1 (+/-2 days)**	**C3 D15 (+/-2 days)**	**C4 D1 (+/-3 days)**	**C5,6 D1 (+/-2 days)**	**C7 D1 (+/-3 days)**	**C8,9 D1 (+/-2 days)**	**C10 D1 (+/-3 days)**	**C11, 12 D1 (+/-2 days)**	**C12 D28 (+/-3 days)**
Informed Consent	X													
Randomization	X													
Pomalidomide po qd[2]		X	X	X	X	X	X	X	X	X[2]	X[2]	X[2]	X[2]	X[2]
History and Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X		X
Confirmation of cGvHD[3]	X													
Body Photography		X								X				
cGVHD 3 Month Trajectory (stable vs. progressive)		X												
Pulmonary Function Testing	X							X		X		X		X
Diagnostic Imaging[4]	X							X		X		X		
Pregnancy Test[5]	X	X	X	X		X		X	X	X	X	X	X	
POMALYST REMS™ program [6]	X	X		X		X		X	X	X	X	X	X	X

Assessments	**Screening**	**BL**						**3 mos**		**6 mos**		**9 mos**		
		BL/ C1 D1	**C1 D15 (+/-2 days)**	**C2 D1 (+/-2 days)**	**C2 D15 (+/-2 days)**	**C3 D1 (+/-2 days)**	**C3 D15 (+/-2 days)**	**C4 D1 (+/-3 days)**	**C5,6 D1 (+/-2 days)**	**C7 D1 (+/-3 days)**	**C8,9 D1 (+/-2 days)**	**C10 D1 (+/-3 days)**	**C11, 12 D1 (+/-2 days)**	**C12 D28 (+/-3 days)**
cGvHD Therapies Recording	X	Throughout the study												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECHO	X													
ECG[7]	X	X		X		X		X		X				
Gynecological Exam		X[14]								X				
Karnofsky Performance Status	X							X		X		X		
CBC w/ differential, platelets[8]		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry[8]		X	X	X	X	X	X	X	X	X	X	X	X	X
CRP, total complement, C3, C4		X		X		X		X		X		X		X
Urinalysis	X							X		X		X		
TSH, free T4	X							X		X		X		
cGvHD Assessment and Response Calculation[9]	X							X		X		X		
AE Monitoring		Throughout the study												

Assessments	**Screening**	**BL**						**3 mos**		**6 mos**		**9 mos**		
		BL/ C1 D1	**C1 D15 (+/-2 days)**	**C2 D1 (+/-2 days)**	**C2 D15 (+/-2 days)**	**C3 D1 (+/-2 days)**	**C3 D15 (+/-2 days)**	**C4 D1 (+/-3 days)**	**C5,6 D1 (+/-2 days)**	**C7 D1 (+/-3 days)**	**C8,9 D1 (+/-2 days)**	**C10 D1 (+/-3 days)**	**C11, 12 D1 (+/-2 days)**	**C12 D28 (+/-3 days)**
Concurrent Drugs	X	Throughout the study												
Skin and Oral Biopsies, saliva collection[10]		X								X				
TBNK		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood and urine for Immunologic Studies[11]		X						X		X		X		X
Blood for PK Studies[12]		X	X	X	X	X	X	X	X	X				
Study drug dispensation/ return/accountability			X	X	X	X	X	X	X	X	X	X	X	X
Rehabilitation medicine		X[14]								X				
Occupational therapy Consults		X[14]						X		X		X		
Dermatology		X								X				
Ophthalmology		X[14]								X				
Schirmer's without anesthesia		X						X		X		X		
NIH Advanced Directives form[15]		X												

[1] Clinic visits can occur ± 3 days. All procedures at protocol-driven time points are performed at the NIH Clinical Center, but if circumstances make this impossible, these data points will be collected in collaboration with referring physicians.

[2] Pomalidomide at assigned doses for 6 months; another 6-month course of treatment will be allowed for patients with response (see Section **3.1.1)**. Only patients who continue therapy beyond 6 months will be required to have clinical monitoring tests during cycles 7 through 12.

[3] Use NIH diagnostic criteria for cGvHD (Appendix C). In addition, use Appendix D for clinical differentiation of acute versus cGvHD.

[4] MRI if indicated and chest CT at baseline and if indicated, at response assessments.

[5] Pregnancy tests for females of childbearing potential must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests must occur 10–14 days and again within 24 hours prior to initiation of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14 days while on therapy (including breaks in therapy), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (see Appendix M).

[6] All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks through the POMALYST REMS™ program. The counseling must be done on at a minimum of every 28 days and at drug discontinuation. See Appendix M.

[7] ECG at indicated intervals baseline, at C2D1, C3D1, C4D1, C7D1 and as clinically indicated. Prolongation of QTc > 0.5 s or QTc interval increases from baseline > 0.06 s is considered as a safety concern.

[8] CBC with differential and platelets, serum chemistries (including sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen [BUN], creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST [SGOT], ALT [SGPT], lactate dehydrogenase [LDH], and uric acid) at least every other week the first 3 months, then monthly until 9 months,then on day 28 of cycle 12. Platelets should be repeated when clinically indicated (e.g., suspected thromboembolic events).

[9] Includes primary and secondary measurement of response, performance scale, global rating, and Lee Symptom Scale (Appendix G through Appendix K).

[10] Skin and oral biopsies and saliva collection will be performed before treatment and after 6 months of pomalidomide, with intent to sample as close to the same area as possible (Section **5.1.1**)

[11] Blood for Immunologic studies will be collected (Section **5.1.2**). A larger 100ml blood (12 R&G CPT) plus a 3ml theophylline citrate blood (for TGFb) will be collected only at baseline, at 3 months (beginning of cycle 4) and the 6 months evaluation (at the end of cycle 6)

[12] For determining serum pomalidomide levels, a 3-mL blood sample will be collected 2 hours (± 15 minutes) after initial oral administration and repeated every 2 weeks (20-24 hours after the last oral dose and 2 hours after the dose) until the 3-month evaluation, point then monthly until the 6-month evaluation (Section **5.1.3**). Pre- dosing PK can be done 18-30 hours post last dose of pomalidomide.

[13] Patients who discontinue study drug for any reason will be followed for survival and cGvHD course and therapy for up to 2 years from the start of study drug (see Section **6.1.3**).

[14] Can be done up to two weeks after starting study drug

[15] As indicated in section **10.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

Patients may undergo additional subspecialty evaluations by Gynecology, Dermatology, Opthalmology, Dentistry, Physical Medicine and Rehabilitation and Occupational Medicine at any additional time points as indicated clinically or during the off study visit per investigator discretion.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.6.1 Criteria for removal from protocol therapy

- Completion of 6- or 12-month course of protocol therapy (depending on the level of response)
- Progressive cGvHD or malignancy requiring new line of systemic therapy
- Participant requests to be withdrawn from active therapy
- Unacceptable toxicity as defined in Section **3.3**
- Dose interruption longer than 35 days
- Positive pregnancy test
- Investigator discretion

The PI is to be notified of all discontinuations from study drug. The reason for dose modification/discontinuation should be recorded in the CRF and in the patient's medical records.

3.6.2 Off-Study Criteria

- Completed 2-year follow-up period
- Subject withdrawal from follow-up period
- Patient lost for follow-up
- Death
- PI decision to end this study

3.6.3 Off Protocol Therapy and OffStudy Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-protocol therapy and when a subject is taken off study. A Participant Status Update Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-l@mail.nih.gov .

4 CONCOMITANT MEDICATIONS/MEASURES

All medications (prescription and non-prescription), treatments and therapies taken throughout the study must be recorded on the appropriate page of the CRF. Patients will be advised to contact the study team before starting any new medications.

4.1 CONCOMITANT CORTICOSTEROID THERAPY AND TAPERING GUIDELINE

During the study, persons may remain on corticosteroids with intent to taper it. A steroid taper will be allowed to begin earliest at 4-6 weeks after starting on protocol, with a 10% (of starting

dose) decrease per week. The study allows maximum two total pulses of steroids with subsequent rapid taper, one at the beginning of pomalidomide therapy in case of GvHD flares associated with the study drug initiation and/or another one later for any flares or worsening of cGvHD symptoms during steroid or other immunosuppression taper. Typical corticosteroid pulse is defined as up to 2 mg/kg/day prednisone or equivalent tapered to the pre-pulse baseline within 3 weeks. Steroid pulses require the PI's approval. If the patient has a GVHD flare and no other reasons to hold the drug for an AE the patient would continue pomalidomide administration concomitantly with steroid pulse. Administration steroid pulses will be carefully recorded in the protocol case report forms.

4.2 OTHER TREATMENTS FOR CGVHD

Patients who are taking concomitant systemic agents for control of cGvHD, such as calcineurin inhibitors (e.g., tacrolimus or cyclosporine) or other immunosuppressants (e.g., mycophenolate or sirolimus) must be on a stable dose in the preceding 4 weeks with an intent to stop if possible after corticosteroids are at stable or supplementation doses (maximum 7.5 mg prednisone/day) or discontinued. Patient should not receive any investigational drugs or initiate any systemic therapy for cGvHD once started on pomalidomide. Patient should not be undergoing extracorporeal photopheresis (ECP) concomitantly with study drug, and if they had ECP in the past, a minimum of 4 weeks should have passed since its discontinuation.

4.3 VENOUS THROMBOEMBOLISM PROPHYLAXIS

Pomalidomide may increase the risk of thrombotic events in persons who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When pomalidomide is combined with other agents such as steroids (e.g., dexamethasone, prednisone), anthracyclines (doxorubicin) and erythropoietin, the risk of thrombosis may be increased. All persons if receiving study treatment in addition to any of these other agents must also agree to take venous thromboembolism (e.g., at minimum aspirin 325 mg/day) or some other form of prophylaxis as deemed appropriate by the PI, such as low molecular weight or unfractionated heparin.[74] Patients should continue to receive anti-thrombotic therapy for the duration of pomalidomide therapy and 5 days after pomalidomide is discontinued.

Because of the increased risk of venous thromboembolism in patients taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

4.4 OTHER ALLOWED CONCOMITANT THERAPY

Ancillary therapy and supportive care considered necessary for the patient's wellbeing may be administered at the discretion of the PI and will follow the NIH Blood and Marrow Transplant Consortium guidelines for supportive care: http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml. Any ancillary or supportive care which may have some effect on efficacy analysis will be carefully recorded in the CRF. Patients

are allowed to take topical steroids at a maximum of 1% hydrocortisone concentration potency equivalence.

4.5 PROHIBITED CONCOMITANT THERAPY

Radiation therapy, cancer chemotherapy, biologic or immunotherapy is prohibited during participation in this study. Concomitant use of other investigational agents is not permitted while persons are receiving study drug.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 Skin Biopsy and Oral Biopsy

Skin and oral research biopsies will be performed before treatment and after 6 months of pomalidomide treatment (with intent to sample as close to the same area as possible) for assessment of sclerotic or lichen-planus like disease by H&E and pathologist evaluation. Immunohistochemistry methods will be applied to look for myofibroblast markers and pSMAD in the sclerotic skin, for T-cell infiltrates, and IFN-induced factors in the oral mucosa and erythematous skin. The advantage of histology is the greater amount of information on cell populations and functional changes in situ of the disease. These biopsies will be obtained by one of the study investigators and processed, stored and analyzed at the ETIB pre-clinical core (Fran Hakim lab). A biopsy sample will be also sent to the NCI pathology laboratory. Patients will have an option to decline such research biopsy and this will not be considered as protocol deviation. Biopsy samples collected on the 04-C-0281 cGvHD natural history study can be also used for these studies if obtained in the timeframe as part of the screening evaluations for this study.

5.1.2 Immunologic Analyses Using Plasma and PBMCs

1. Blood: Blood will be collected, and PBMC and plasma will be cryopreserved for later batch analyses of markers relevant to cGvHD activity. Plasma will be collected with theophylline-citrate anticoagulant (to prevent platelet breakdown) for assessment of TGFb and PDGF, which may be relevant to fibrosis. Heparinized plasma will be assayed for markers of cGvHD activity (including but not limited to BAFF, and IFN-induced chemokines). PBMC will be cryopreserved for subsequent flow cytometry of cell populations and sorting of monocytes for transcriptional analysis of genes upregulated in active cGvHD. The primary collection of blood for these analyses of pomalidomide effect on cGvHD will be at baseline and at 3 and 6 month evaluation time point. At these three timepoints one theophylline citrate plasma tube (for TGFb) and 12 red and green topped heparin CPT tubes (total of 100 cc) will be collected; a final collection will be done on patients continuing treatment until 12 months.
2. Plasma will be assayed for BAFF, IFN-induced chemokines and MCP-1. Separate collection of theophylline-citrate blood (different anticoagulant to prevent platelet breakdown) will be performed for assessment of TGFb and PDGF.
3. Monocyte transcriptome: Monocytes will be sorted from PBMC for Nanostring evaluation of the monocyte transcriptome. This would be done on cryopreserved cells at

the end of the study. Monocytes circulate throughout the body, are responsive to a variety of cytokines in tissues affected by cGvHD and maybe therefore serve as a reporter for changes in cGvHD-affected tissues.

4. Lymphocyte populations. Changes in circulating populations of lymphocytes will be assessed by flow cytometry on whole blood to determine changes in CD3, CD4, CD8, B and NK populations. At baseline, at the start of each cycle up to the 3 month time point and at 6 and 12 months, one 3ml lavender (EDTA) tube will be drawn and lymphophenotyping will be performed using Clinical center's CLIA certified Immunophenotyping panel and reported in the CRIS. Further research assessments of the percentages of regulatory T cells, of naïve, memory and effector T cells and of B cell transitional, naïve and memory populations will be done in the ETIB Preclinical Core (Fran Hakim) on the baseline and at 3 month evaluation time points until 12 months post enrollment. Active cGvHD has been associated with decreases in Treg populations, reduced thymopoiesis (fewer naïve T cells) and increases in CD21- transitional B cell populations. Urine will be collected at 3 month intervals for assessment of biomarkers in urine as compared with blood.

The assays indicated are designed to assess the alterations in skin, oral mucosa and in circulating lymphocytes and plasma that may result from pomalidomide. If there is a decline in TGFb production or response, then this may be evident in TGFb levels in the plasma and in degree of fibrosis (by pathologist evaluation) and extent of pSMAD2/3 in sclerotic skin. If there is an increase in Th1 cells or a shift in Treg populations, this may be reflected in circulating T cell populations, plasma cytokines and tissue infiltrates.

5.1.3 Measurement of Pomalidomide Serum Levels

The objective of measuring pomalidomide serum levels is for the documentation of systemic absorption. A 6-mL blood sample will be collected 2 hours (+/- 20 minutes, exact time elapsed post-dosing will be recorded on PK sheets) after initial oral administration and repeated peak and trough every 2 weeks (20-28 hours after the last oral dose and 2 hours post-dose) until the 3-month evaluation, then monthly until the 6-month evaluation. Pre- dosing PK can be done 18-30 hours post last dose of pomalidomide. Actual dosing dates and times will be recorded. Detailed instruction for sample collection, processing, storage, and handling can be found in Appendix B. These sample collections will occur at the protocol scheduled evaluation visits at the NIH Clinical Center.

The determination of pomalidomide concentrations in plasma samples, as well as the pharmacokinetic data analysis, will be performed by the Clinical Pharmacology Program (Dr. William Figg, Head, 301-402-3623). Samples will be analyzed using a validated LC-MS/MS method.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.2.1 ETIB Procedures

Blood and tissue samples, collected for the purpose of research under IRB-approved protocols of the Experimental Transplantation and Immunology Branch will be stored and may be archived by the ETIB Preclinical Service, with the exception of blood samples for pomalidomide analysis,

which will be stored separately by the Clinical Pharmacology Program (CPP) until analysis. All data associated with archived clinical research samples is entered into the ETIB Preclinical Service's Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB Preclinical Service folder. Access to this folder is limited to ETIB clinical staff, requiring individual login and password. All staff in the Preclinical Service laboratory have received annually updated NIH/CIT training and maintain standards of computer security.

The data recorded for each sample includes the patient ID, name, trial name/protocol number, date drawn, treatment cycle/posttransplant time point, cell source (e. g. peripheral blood, lymphapheresis, mobilized peripheral blood stem cells, marrow, oral biopsy) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI/ETIB clinical records or NCI C3D. All samples currently receive a unique bar code number, which is included in the Preclinical Service Stored Sample database. Only this bar code will be recorded on the sample vial, and the vials will not be traceable back to patients without authorized access to the Preclinical Service database.

Samples are stored in locked freezers at -85°C (sera and plasma) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at the Preclinical Service laboratory (12C216). Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol or through his/her submission and IRB approval of the NCI IRB Authorization Form stipulating whether IRB review is not necessary or IRB approval is granted for the pursuit of this new research activity. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with objectives of the original protocol for which the samples were collected, or (using only unlinked or coded samples) for an IRB-approved protocol as stipulated on the IRB Authorization Form, and that any unused samples must be returned to the Preclinical Service laboratory.

5.2.1.1 Protocol Completion/Sample Destruction

Once primary research objectives for the protocol are achieved, researchers can request access to remaining samples, providing they have both approval of the Principal Investigator of the original protocol under which the samples or data were collected and either an IRB-approved protocol and patient consent or the IRB Authorization Form stipulating that the activity is exempt from IRB review. Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the Preclinical Service laboratory.

The Preclinical Service staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (e.g., broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher. The Principal Investigators will annually report this information to the IRB.

5.2.2 Clinical Pharmacology Program Procedures

All samples sent to the Clinical Pharmacology Program (CPP) will be barcoded, with data entered and stored in the Patient Sample Data Management System (PSDMS) utilized by the CPP. This is a secure program, with access to the PSDM System limited to defined CPP personnel, who are issued individual user accounts. Installation of PSDMS is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

All CPP personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.2.2.1 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the CPP and offsite at NCI Frederick Central Repository Services (Fisher Bioservices) in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in the PSDM System. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the CPP. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the PSDMS.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data will be prospectively collected and entered into an NCI C3D Database using pre-designed CRFs. All persons must have signed an Informed Consent and have an on-study confirmation of eligibility form completed before entering on the study. Complete records will be maintained on each patient including the hospital chart with any supplementary information obtained from outside laboratories, radiology reports, or physician's records. These records will be the primary source documents that form the basis for the research record. The primary source documentation

will assure the availability of the following: on-study information, including patient eligibility data and patient history; flow sheets, specialty forms for pathology, radiation, or surgery; and off-study summary sheet, including a final assessment by the treating physician. An enrollment log will be maintained in the regulatory binder/file which is the only location of personal identifiers with unique subject identification number.

All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.1.1 Eligibility Checklist

The eligibility checklist is to be completed at study entry and forwarded to protocol research nurse who will forward the checklist to the Central Registration Office.

6.1.2 Protocol Deviations and Non-Compliance

Any protocol non-compliance or deviations should be directly reported to the PI (Steven Pavletic, 240-760-6174, pavletis@mail.nih.gov) and to the NCI IRB per Section **7.2**.

6.1.3 Follow-up

All persons will be followed for SAEs for 30 days after last dose of pomalidomide. Patients who discontinue therapy for any reason will be invited for a follow up visit at 3 months after last dose, then followed up by a phone call to the patient and/or the primary physician's office at 12 and 24 months after starting the first dose of pomalidomide. The phone call will focus on a) survival status and cause of death if pertinent, b) ongoing systemic treatment for cGvHD and date of discontinuation, c) primary malignancy progression, d) any second primary malignancy, e) return to work part-time or full-time. Primary and contributing causes of death are to be recorded in the CRF and the patient's medical record.

6.2 RESPONSE CRITERIA

6.2.1 Definitions

Evaluable for efficacy: Patients who complete 6 months of therapy will be evaluable for the secondary endpoint of efficacy assessment. Patients who progress earlier will be also included in the analysis of efficacy.

6.2.2 Efficacy Analysis

The primary evaluation point is overall response at 6 months using the NIH cGvHD response criteria measures.[29] The overall response score will be assessed as CR, PR, SD or PD as per NIH guidelines. The organ-specific and other subcomponents of the overall response score will be analyzed individually and absolute values recorded.

Up to 2 corticosteroid pulses will be allowed, one for initial flares and one for late flares as described in Section **4.1.**

Response will be assessed every 3 months from the start of pomalidomide. To ensure comparability, baseline and on-study methods for response assessment will be performed using identical grading, scale or techniques. The Chronic GVHD Assessment (Clinician) Form will be completed at each 3-month evaluation visit [Appendix G]. Included in that form are both organ-specific primary measurements and clinician-assessed secondary measurements. The response of each affected organ will be evaluated and an overall response (CR, PR, stable disease) will be determined.

6.2.2.1 Response Criteria

Efficacy will be assessed using NIH consensus criteria measuring for therapeutic response in clinical trials for cGvHD[29]:

- **CR** is defined as complete resolution in all of signs and symptoms at all affected organs or tissues.
- **PR** is defined as improvement in ≥ 1 organ or tissue with no progression in any other affected organ or tissue. The calculations for PR and progressive disease (PD) are provided in Appendix H and Appendix I.
- **Response < PR** is defined as change towards improvement from the pre-treatment baseline but not meeting the criteria for CR or PR.
- **Stable Disease** is defined as no change in cGvHD, SD will be considered as response in patients with documented cGvHD progression over preceding 3 months.
- **Flare** is defined as exacerbation of cGvHD manifestations during withdrawal of immunosuppressive therapy which do not exceed those at the beginning of the trial and improves after reinstatement of previous treatment.
- **Progressive disease** is defined as failure of therapy to control cGvHD. The calculations for progressive disease (PD) are provided in Appendix I. Assessment by Organ-Specific Criteria. Patients who progress prior to 6 months evaluation will be also evaluable for the primary efficacy endpoint.
- **Mixed response** (improvement in some organs but worsening in others) will be categorized as progressive disease.

As outlined in Section **3.5**, type of involved organ, location and its measurements will be recorded at scheduled evaluations and reported on the appropriate CRF, equal to "Chronic GVHD Assessment (Clinician) Form," (Appendix G). All other measurements not being included in primary assessment but clinically related to cGvHD (e.g., change of pigmentation) will be reported in the source documents.

Skin and skin appendages: Skin assessments include 4 anatomic level of skin involvement:

(1) erythematous rash (epidermal),

(2) movable sclerosis (dermal),

(3) non-moveable sclerosis, hidebound skin, or involvement of subcutaneous tissue and fascia (subcutaneous) and

(4) ulceration (full thickness loss of epidermal tissue).

The first 3 measurements should be taken separately and recorded in metric notation using a body surface area (BSA). A cutaneous assessment worksheet for recording the BSA is provided (Appendix J). The size of ulcer should be measured the longest diameter (LD) of the largest ulcer.

Eyes: The primary measurement of lacrimal gland function in cGvHD is using the Schirmer's test. The test should be performed without anesthesia for both eyes (OU) unless physically inapplicable. The measurement of each eye and the average of measurements will be recorded in the CRF.

Mouth: Mouth assessments include:

(1) mucosal erythema by 0-3 grading based on the color intensity, (2) lichen-type hyperkeratosis by 0-3 grading based on the percentage of oral surface area,(3 ulceration by 0-6 based on percentage of oral surface area, and (4) mucoceles by 0-3 grading based on its total number of presence.

Hematopoietic: The measurements of hematopoietic response include:

(1) platelet count,

(2) eosinophil count and percentage.

White blood cell (WBC) count will be recorded on the Assessment Form but will not be used for response assessment.

Gastrointestinal tract: Gastrointestinal (GI) symptoms are graded through interview by the investigator according to 0-3 severity scales.

Liver: Involvement of liver is graded according to the levels of bilirubin and liver enzymes (AST and ALT).

Lung: The forced expiratory volume in the first second (FEV1) and single breath diffusion lung capacity for carbon monoxide (DLCO) is included as components for the lung function score (LFS). LFS is computed by the extent of FEV1 and DLCO compromise (>80% = 1, 70 – 79% = 2, 60 – 69% = 3, 50 – 59% = 4, 40 – 49% = 5, <40% = 6). Scores for FEV1 and DLCO are added and the sum reduced to an overall category according to following table (Table 5). Absolute values of both FEV1 and DLCO should be recorded in the CRF.

Table 5. Categories of the Lung Function Score

Category	Lung Function	Lung Function Score
I	Normal	2
II	Mild decrease	3 – 5
III	Moderate decrease	6 – 9
IV	Severe decrease	10 – 12

Global chronic GVHD Rating: The overall clinical impression of patient's cGvHD will be recorded on a 4-point (0-3) scale on the Chronic GVHD Assessment (Clinician) Form.

Chronic GVHD Improvement Scale: The overall changes of patient's cGvHD symptoms during previous 3 months will be recorded on a 7-point (-3 to +3) scale on the Chronic GVHD Assessment (Clinician) Form.

Chronic GVHD Symptom Severity Scale: The overall severity of patient's cGvHD symptoms will be recorded on an 11-point (0-10) numeric scale on the Chronic GVHD Assessment (Clinician) Form.

Karnofsky Performance Scale: The Karnofsky Performance Scale will be only recorded on the Chronic GVHD Assessment (Clinician) Form but not used as a measure of response.

Lee symptom scale was developed as a 30-item symptom scale with 7 subscales to capture the cGvHD-specific symptom burden (Appendix K). This symptom scale showed to correlate with persons' self-assessed mild, moderate, and severe cGvHD manifestations in cross-sectional validation analysis. "Lee total score" will be calculated per Lee et al.[75] Longitudinal assessments showed that changes in overall health status correlated best with changes in quality of life as measured by the SF-36 and FACT-BMT. We will not use "Lee symptom scale" as a measure of pomalidomide efficacy but as supplemental information on the quality of life.

NIH organ 0-3 scoring (Appendix E) will be also collected at the evaluation endpoints.[22] Although not initially developed for response assessments, the evidence is emerging in some domains (skin, eyes) about potential use of this scale as a simple and valid assessment of cGvHD change over time.

6.2.2.2 Summary of Response Measures

i. Primary response measures

1. Skin (BSA), erythema, moveable, non-moveable
2. Eyes (Schirmer)
3. Mouth (modified OMRS)
4. Liver (bilirubin, AST, ALT)
5. GI tract (GI response scale)
6. Lung (FEV, DLCO, LFS)
7. Clinician assessment scale (3-point, 7-point change, 11-point global)
8. ROM visual Carpenter scale (1-7 and 1-4)
9. NIH organ scoring

ii. Secondary assessments

1. Platelet count, CRP, C3, C4, albumen

2. 2 and 6 minute walk time
3. Grip strength
4. Lee symptom scale
5. HAP, SF-36, Karnofsky
6. MRI (if positive baseline)
7. Disabilities of the Arm Hand and Shoulder (DASH)

6.2.2.3 Other endpoints to be recorded at the evaluation time points: Need for secondary systemic therapy for GvHD, malignancy progression, discontinuation of immune suppression, steroid doses, other immunosuppressive drug doses, intensity of immunosuppression, NIH global severity (Appendix P), survival, progression-free/malignancy-free survival, disability-free survival.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **6.1**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **7.2**, **7.3** and **7.4.**

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction 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; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subject.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

7.2.1 NCI-IRB and NCI Clinical Director Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and the NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

    NOTE: Grade 1 events are not required to be reported.

7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an Unanticipated Problem will need to be reported to the NCI IRB.

7.2.4 Request for waiver from IRB reporting

We are requesting a waiver for the expedited reporting of deviations related to study drug regimen adherence. Patient non-adherence to study medication administration will only be reportable if greater than 15% of the doses are missed for any given cycle. It is expected that approximately 30% of patients will not be compliant with doses. Should the rate of non-adherence exceed 30%, this will be reported to the IRB as an unanticipated problem.

Chronic GVHD is a chronic multi-organ disease which lasts for many years. Non-compliance is a common reality in this patient population and overly restrictive criteria for missing doses would make this treatment study execution very difficult. Equally, the therapy trajectory is very long – 6-12 months and it is estimated based on our prior experiences that proposed % of tolerance for non-reporting would not affect substantially the expected immunomodulatory therapeutic effects in this slowly moving disease therefore would not create the threshold criteria for protocol deviation.

7.3 IND SPONSOR REPORTING CRITERIA

An investigator must immediately report to the sponsor using the mandatory MedWatch form 3500a, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

- All Grade 5 (fatal) events (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.

- All other serious adverse events including deaths due to progressive disease must be reported within one business day

Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Events will be submitted to the Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov, and to the CCR PI and study coordinator.

7.3.1 Reporting Pregnancy to IND Sponsor

7.3.1.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and the pregnancy reported to the Sponsor. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form "Describe Event or Problem".

Pregnancy itself is not regarded as an SAE. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that pregnancy should be reported in an expedited manner as **Grade 3** "***Pregnancy, puerperium and perinatal conditions - Other (pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.3.1.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 28 days after the last dose of Pomalidomide.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 28 days after the last dose should, if possible, be followed up and documented.

7.4 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

All events listed below must be reported in the defined timelines to CCRsafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The **Celgene tracking number (PO-GvHD-NCI-0046)** and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

7.4.1.1 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on pomalidomide, or within 30 days of the subject's last dose of pomalidomide, are considered immediately reportable events. Pomalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to pomalidomide should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking pomalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

7.5 DATA AND SAFETY MONITORING PLAN

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis, once a week when persons are being actively treated on the trial, to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior persons.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 Sponsor Monitoring Plan

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

8 THIS TRIAL WILL BE MONITORED BY PERSONNEL EMPLOYED BY AN NCI CONTRACTOR. MONITORS ARE QUALIFIED BY TRAINING AND EXPERIENCE TO MONITOR THE PROGRESS OF CLINICAL TRIALS. PERSONNEL MONITORING THIS STUDY WILL NOT BE AFFILIATED IN ANY WAY WITH THE TRIAL CONDUCT. STATISTICAL CONSIDERATIONS

It is known from prior trials that the pomalidomide MTD is about 3 mg/d in persons with bone marrow disorders receiving therapies for cancer. Due to high frequency of pomalidomide dose de-escalation observed in preliminary cGvHD experiences when given at 3 mg/d, this study will explore clinical toxicity of gradual escalation doses below 3.0 mg.

The primary objective of this study is to determine if patients with cGVHD will experience an acceptable level of clinical response when treated with either a constant low dose of pomalidomide (0.5 mg/day) for six months or a strategy of increasing dose of pomalidomide from 0.5 mg/d up through each individual patients' maximum tolerated dose, with escalations by 0.5 mg/d every 2 weeks to a maximum of 2.0 mg/d. The study will thus randomize patients between fixed low dose and escalating dose to tolerance, and will be considered a randomized phase II trial with a selection design component.

In each of the two arms, the trial will be conducted using a single stage design. With 16 patients on each arm, an exact binomial test would have 90% power to detect a difference between a 5% response rate and a 30% response rate using a 0.10 one-sided significance level and an exact binomial test. In addition, after the trial has ended, the 80% and 95% confidence limits will be determined for each arm about the observed response proportion in order to aid in interpretation of the results. If there are 3 or more responses in 16 patients, this would be sufficient to rule out a 5% response rate and demonstrate consistency with 30% or better response rates.

At the conclusion of the study, if both arms are able to accrue to the full 16 patients, the arm with the greater number of responses will be selected for further investigation subsequently. That is, if the fixed, low-dose arm, or the increasing dose level arm, has the greater number of responses, then that arm would be studied further. In the event of a tie, the lower dose arm would likely be preferred. As an example, if the true probabilities of response on the two arms were 0.10 and 0.30, then the probability of correctly selecting the superior arm would be 93%, and if the true probabilities on the two arms were 0.15 and 0.30, the probability of correct selection would be 84%.

As an early stopping rule for futility, if after 7 patients have enrolled on either arm, 0 have responded, then no further patients will be accrued to that arm as soon as this can be determined. In practice, this means that patients may continue to be accrued beyond 7 in an arm, but no more patients would be registered and treated on that arm once the first 7 were evaluated and no PRs or CRs were identified in those first 7.

To protect patient safety, an early stopping rule will be implemented as follows. For patients treated on either arm, if 2 patients in the first 6, or 33% of the patients at any time experience a DLT at a given dose level, no further patients will be treated at that given level on the trial. Furthermore, when more than 6 patients have received a given dose level, if at any time 33% or more patients experience a DLT when treated at that dose level, then no further patients will be treated at that dose level. Thus, as an example, should there be 2 patients with a DLT in the first 6 who are able to receive 2.0 mg/day on the dose escalating arm, then subsequent patients treated on that arm will not be escalated beyond 1.5 mg/day.

With two arms, each of which has a maximal accrual of 16 patients, up to 32 evaluable patients will be randomized. In order to allow for a very small number of patients who are not able to be evaluated at all for response, the accrual ceiling will be set at 35.

9 COLLABORATIVE AGREEMENTS

9.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

Pomalidomide is provided by Celgene Corporation under CRADA # 02328 Celgene/NCI Clinical Research Leader: "Preclinical and Clinical Development of Celgene Corporation's Proprietary Immunomodulatory Agent, CC4047 (Pomalidomide), as a Therapy for Graft-Versus-Host Disease (GVHD)," executed July 13, 2010.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

No subjects will be excluded from participation based on gender, race or ethnicity. The study will be open to all subjects who satisfy the inclusion criteria and provide an informed consent to the protocol.

10.1.1 Recruitment

Subjects will be recruited from NIH Clinical Center hematopoietic stem cell transplant clinics but could be referred from the outside institutions. Study participants will be primarily recruited from the 04-C-0281 cGvHD natural history study protocol, which currently has more than 260 persons registered and enrolls approximately 3 persons per month, most of them with moderate or severe cGvHD. Referrals will be also accepted from the other NIH protocols or from the extramural community. Every effort will be made to screen potential candidates through the existing 04-C-0281 natural history protocol, which is a non-therapeutic study as part of pre-enrollment evaluations. The patient population enrolled on this study is expected to be representative of the population of persons receiving allogeneic hematopoietic stem cell transplantation at the NIH and nationwide.

10.2 PARTICIPATION OF CHILDREN

As there is no experience with pomalidomide in children, this study will be limited to subjects age 18 years or older.

10.3 PARTICIPATION OF NIH SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH

Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 Evaluation of Benefits and Risks/Discomforts

10.4.1 Related to Pomalidomide

Potential risks of pomalidomide include the range of toxicities described in Section **11.1.9** and the consent form. There may also be unexpected side effects. All subjects will be carefully monitored for side effects.

10.4.2 Related to Blood Collection

Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, or infections may rarely occur.

10.4.3 Related to Tissue Biopsy

Skin and oral punch biopsy is a minor surgical procedure that may be associated with temporary bleeding, hematoma at the site, local infection and postoperative discomfort. These risks are small (generally <5%) and transient.

10.4.4 Related to Pregnancy

Pomalidomide is in a class of agents that is known to be teratogenic. Women of child-bearing potential and men must agree to adhere to methods of contraception and other fertility control measures as prescribed by the protocol. This will include counseling about pregnancy precautions and the potential risks of fetal exposure conducted at a minimum of every 28 days. Women of child-bearing potential must also undergo regular pregnancy testing.

10.5 Risks/Benefits Analysis

Risks of participating in this trial include side effects from pomalidomide and risks of medical procedures (blood draws, oral and skin biopsy). Patients may receive benefit from the clinical monitoring or potentially experience improvement in cGvHD symptoms or quality of life. Therefore, this research represents more than minimal risk to subjects with prospect of direct benefit to individual subjects.

10.6 Consent Process and Documentation

The investigational nature and research objectives of this trial, the procedure and its attendant risks and discomforts will be carefully explained to the subject. The potential subject will be educated regarding the nature of the condition, proposed intervention, and outcome measures. Study subjects will be informed that participation is entirely voluntary and that withdrawal from the study can be made at any time without penalty of benefits to which they may be entitled. Informed consent will be obtained by Dr. Steven Pavletic or his designee. At any time during participation in the protocol if new information becomes available relating to risks, adverse events, or toxicities, this information will be provided orally or in writing to all enrolled or

prospective participants. Documentation will be provided to the IRB and if necessary the informed consent amended to reflect relevant information.

10.6.1 Telephone re-consent procedure

Reconsent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

10.6.2 Short form consent process for non-English speaking patients

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

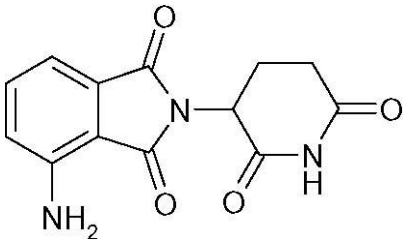
We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

11 PHARMACEUTICAL INFORMATION

11.1 POMALIDOMIDE

11.1.1 Description

Pomalidomide, 4-amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1'-one)-1,3-dione, is a novel immunomodulatory drug. The Chemical Abstract Service (CAS) registry number for pomalidomide is 19171-19-8. Pomalidomide is also known as CC-4047. The chemical structure of the active pharmaceutical ingredient is as follows:



Pomalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S (-) and R (+). Pomalidomide is being developed as a racemate.

Pomalidomide shares a number of the beneficial pharmacologic properties of thalidomide and lenalidomide, but it is a more potent anti-proliferative immunomodulating agent than either drug.

11.1.2 Source

Celgene Corporation will supply pomalidomide 0.5 mg, 1.0 mg, and 2.0 mg capsules. Pomalidomide will be packaged in bottles containing capsules for 28 days of every 28-day cycle. Only a 28-day supply of pomalidomide may be provided to the patient for each 28-day cycle. Site will utilize commercial supply of anti-thrombotic agents for prophylactic purposes.

Celgene will supply drug free of charge. The initial drug shipment will be sent to NIH pharmacy. NIH pharmacy will order all subsequent drug orders.

11.1.3 Formulation and Preparation

Pomalidomide will be administered as 2.0 mg, 1.0 mg and/or 0.5 mg capsules to be taken orally. Each daily dose of pomalidomide should be taken at approximately the same time of day. No modification of capsules is necessary.

11.1.4 Study Drug Packaging and Labeling

Pomalidomide investigational supplies are dispensed to the persons in individual bottles of capsules. Each bottle will identify the contents as study medication. The label for study drug supplied by Celgene will bear the Celgene Corporation name and address, the protocol number, the quantity of study drug contained, and the standard caution statement, as follows: “Caution: New Drug - Limited by Federal Law to Investigational Use.”

Pomalidomide should not be handled by FCBP unless wearing gloves. All bottles will contain the following warning label: “WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS.”

11.1.5 Study Drug Receipt and Storage

The PI is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The PI or their designee will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

11.1.6 Administration Procedures

Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves. Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal.

If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up, rather it should be taken at the next scheduled time point.

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

Accurate recording of all study drug administration (including dispensing and dosing) will be made in the source documents.

11.1.7 Study Drug Accountability

The PI or designee(s) is responsible for accounting for all study drug that is issued to and returned by the patient during the course of the study.

11.1.8 Study Drug Handling and Disposal

Celgene will instruct the Investigator(s) on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the patient's CRF and source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules.

11.1.9 Expected Toxicities

Likely (more than 20%): Constipation, fatigue, myalgia, and rash.

Less Likely (less than 20%): Anemia, thrombocytopenia, neutropenia, productive cough, dyspnea (with or without exertion), lung pain, nose bleeds, sore throat, discolored sputum, bloody sputum, irritation of the upper respiratory tract, other respiratory infections, fever, headache, bacterial or viral infections, bone pain, muscle cramps, joint swelling, parasthesias, nausea, diarrhea, bloating, dry mouth and irritation of the mouth, dry skin, redness of the skin, and itching, unusual weakness or dizziness, hypotension, flushing, and chest pain.

Rare (Less than 3%): pneumonia, vomiting, blood clots in persons receiving combination therapy with other cancer drug, erythropoeitin, and/or steroids.

Experience with pomalidomide in humans and animals is detailed in the background section. Neutropenia was the most frequently reported grade 3/4 AE in subjects with relapsed/refractory multiple myeloma. The majority of these occurred without associated infection and was the dose-limiting toxicity observed during the dose finding portion of the study. Neutropenia was also the most frequently reported AE and SAE in subjects with multiple myeloma followed by thrombocytopenia and anemia. Subjects receiving pomalidomide have developed venous thromboembolic events (DVTs and pulmonary emboli) reported as SAEs. Anticoagulant prophylaxis is recommended as a precaution per protocol.

Pomalidomide was found to be teratogenic in a developmental study in rabbits. Precautions against fetal exposure are detailed throughout the protocol.

11.1.10 Incompatibilities

Based on in vitro metabolism data, pomalidomide is not likely to precipitate drug-drug interactions especially due to inhibition or induction when co-administered with cytochrome P-450, substrates.

A food effect study with pomalidomide has not been conducted.

12 REFERENCES

1. Lee SJ VG, Flowers ME. Chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2003;9(4):215-233.
2. Lee SJ KJ, Barrett AJ, Ringden O, Antin JH, Cahn JY, Carabasi MH, Gale RP, Giralt S, Hale GA, Ilhan O, McCarthy PL, Socie G, Verdonck LF, Weisdorf DJ, Horowitz MM. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood.* 2002;100(2):406-414.
3. Filipovich AH WD, Pavletic S, Socie G, Wingard JR, Lee SJ, Martin P, Chien J, Przepiorka D, Couriel D, Cowen EW, Dinndorf P, Farrell A, Hartzman R, Henslee-Downey J, Jacobsohn D, McDonald G, Mittleman B, Rizzo JD, Robinson M, Schubert M, Schultz K, Shulman H, Turner M, Vogelsang G, Flowers ME. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant.* 2005;11(12):945-956.
4. Vogelsang GB PS. *Chronic Graft Versus Host Disease*

Interdisciplinary Management. Cambrige University Press; 2009.

5. Pavletic SZ CS, Kernan NA, Henslee-Downey J, Mendizabal AM, Papadopoulos E, Gingrich R, Casper J, Yanovich S, Weisdorf D. Influence of T-cell depletion on chronic graft-versus-host disease: results of a multicenter randomized trial in unrelated marrow donor transplantation. *Blood.* 2005;106(9):3308-3313.
6. Baird K PS. Chronic graft versus host disease. *Curr Opin Hematol.* 2006;13(6):426-435.
7. Socie G RJ, Martin PJ. Current challenges in chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2010;16:146-151.
8. Le NT CN. Regulating regulatory T cells. *Bone Marrow Transplant.* 2007;39(1)::1-9.
9. Koreth J, Matsuoka K, Kim HT, et al. Interleukin-2 and regulatory T cells in graft-versus-host disease. *N Engl J Med.* 2011;365(22):2055-2066.
10. Skert C DD, Michelutti A, Patriarca F, Arpinati M, Filì C, Lucchi P, Malagola M, Bergonzi C, Roccaro A, Peli A, Ricotta D, Caimi L, Fanin R, Baccarani M, Russo D. Kinetics of Th1/Th2 cytokines and lymphocyte subsets to predict chronic GVHD after allo-SCT: results of a prospective study. *Bone Marrow Transplant.* 2009;44(11):729-737.
11. Barak V L-SF, Nisman B, Nagler A. Cytokine dysregulation in chronic graft versus host disease. *Leuk Lymphoma.* 1995;17((1-2)):169-173.
12. Liem LM FW, van Houwelingen HC, Goulmy E. Serum transforming growth factor-beta1 levels in bone marrow transplant recipients correlate with blood cell counts and chronic graft-versus-host disease. *Transplantation.* 1999;67(1).
13. Bogunia-Kubik K MA, Wysoczanska B, Lange A. Recipient interferon-gamma 3/3 genotype contributes to the development of chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Haematologica.* 2005;90(3):425-426.

14. Zhang C TI, Zhang Z, Liu Y, Kandeel F, Forman S, Strober S, Zeng D. Donor CD4+ T and B cells in transplants induce chronic graft-versus-host disease with autoimmune manifestations. *Blood.* 2006;107(7):2993-3001.

15. Trendelenburg M GM, Passweg J, Tichelli A, Tyndall A, Gratwohl A. "Altered immunity syndrome", a distinct entity in long-term bone marrow transplantation survivors? *Bone Marrow Transplant.* 2001;28(12):1175-1176.

16. Patriarca F SC, Sperotto A, Zaja F, Falleti E, Mestroni R, Kikic F, Calistri E, Filì C, Geromin A, Cerno M, Fanin R. The development of autoantibodies after allogeneic stem cell transplantation is related with chronic graft-vs-host disease and immune recovery. *Exp Hematol.* 2006;34(3):389-396.

17. Svegliati S OA, Campelli N, Luchetti M, Poloni A, Trappolini S, Moroncini G, Bacigalupo A, Leoni P, Avvedimento EV, Gabrielli A. Stimulatory autoantibodies to PDGF receptor in patients with extensive chronic graft-versus-host disease. *Blood.* 2007;110(1):237-241.

18. Sarantopoulos S SK, Kim HT, Bhuiya NS, Cutler CS, Soiffer RJ, Antin JH, Ritz J. High levels of B-cell activating factor in patients with active chronic graft-versus-host disease. *Clin Cancer Res.* 2007;13(20):6107-6114.

19. Fujii H CG, She K, Aslanian S, Shimizu H, Kariminia A, Krailo M, Chen Z, McMaster R, Bergman A, Goldman F, Grupp SA, Wall DA, Gilman AL, Schultz KR. Biomarkers in newly diagnosed pediatric-extensive chronic graft-versus-host disease: a report from the Children's Oncology Group. *Blood.* 2008;111(6):3276-3285.

20. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood.* 2006;108(2):756-762.

21. Bhushan V, Collins RH, Jr. Chronic graft-vs-host disease. *JAMA.* 2003;290(19):2599-2603.

22. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant.* 2005;11(12):945-956.

23. Lee SJ. New approaches for preventing and treating chronic graft-versus-host disease. *Blood.* 2005;105(11):4200-4206.

24. Shlomchik WD. Graft-versus-host disease. *Nat Rev Immunol.* 2007;7(5):340-352.

25. Shlomchik WD, Lee SJ, Couriel D, Pavletic SZ. Transplantation's greatest challenges: advances in chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2007;13(1 Suppl 1):2-10.

26. Wolff D, Schleuning M, von Harsdorf S, et al. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant.* 2011;17(1):1-17.

27. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: national institutes of health consensus development project on criteria for clinical trials in chronic Graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant.* 2006;12(4):375-396.

28. Martin PJ, Weisdorf D, Przepiorka D, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease:

VI. Design of Clinical Trials Working Group report. *Biol Blood Marrow Transplant.* 2006;12(5):491-505.

29. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant.* 2006;12(3):252-266.

30. Schultz KR, Miklos DB, Fowler D, et al. Toward biomarkers for chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: III. Biomarker Working Group Report. *Biol Blood Marrow Transplant.* 2006;12(2):126-137.

31. Shulman HM, Kleiner D, Lee SJ, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. *Biol Blood Marrow Transplant.* 2006;12(1):31-47.

32. Flowers ME, Martin PJ. Evaluation of thalidomide for treatment or prevention of chronic graft-versus-host disease. *Leuk Lymphoma.* 2003;44(7):1141-1146.

33. Flowers ME, Storer B, Carpenter P, et al. Treatment change as a predictor of outcome among patients with classic chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2008;14(12):1380-1384.

34. Flowers ME MP. Evaluation of thalidomide for treatment or prevention of chronic graft-versus-host disease. *Leuk Lymphoma.* 2003;44(7):1141-1146.

35. Martin PJ, Inamoto Y, Carpenter PA, Lee SJ, Flowers ME. Treatment of chronic graft-versus-host disease: Past, present and future. *Korean J Hematol.* 2011;46(3):153-163.

36. Vogelsang GB FE, Hess AD, Altamonte V, Beschorner WE, Jabs DA, Corio RL, Levin LS, Colvin OM, Wingard JR, et al. Thalidomide for the treatment of chronic graft-versus-host disease. *N Engl J Med.* 1992;326(16):1055-1058.

37. Tefferi A VS, Barosi G, Passamonti F, Roboz GJ, Gisslinger H, Paquette RL, Cervantes F, Rivera CE, Deeg HJ, Thiele J, Kvasnicka HM, Vardiman JW, Zhang Y, Bekele BN, Mesa RA, Gale RP, Kantarjian HM. Pomalidomide is active in the treatment of anemia associated with myelofibrosis. *J Clin Oncol.* 2009;27(27):4563-4569.

38. Heney D ND, Wheeldon J, Bailey CC, Lewis IJ, Barnard DL. Thalidomide treatment for chronic graft-versus-host disease. *Br J Haematol.* 1991;78(1):23-27.

39. Rovelli A AC, Nesi F, Balduzzi A, Nicolini B, Locasciulli A, Vassallo E, Miniero R, Uderzo C. The role of thalidomide in the treatment of refractory chronic graft-versus-host disease following bone marrow transplantation in children. *Bone Marrow Transplant.* 1998;21(6):577-581.

40. Forsyth CJ, Cremer PD, Torzillo P, Iland HJ, Young GA. Thalidomide responsive chronic pulmonary GVHD. *Bone Marrow Transplant.* 1996;17(2):291-293.

41. Staumont-Salle D, Magro L, Piette F, Thomas P, Jouet JP, Catteau B. Chronic graft-versus-host disease revealed by lichenoid vulvar lesions successfully treated with thalidomide. *Acta Derm Venereol.* 2003;83(4):302-303.

42. Browne PV WD, DeFor T, Miller WJ, Davies SM, Filipovich A, McGlave PB, Ramsay NK, Wagner J, Enright H. Response to thalidomide therapy in refractory chronic graft-versus-host disease. *Bone Marrow Transplant.*;26(8):865-869.

43. Cole CH RP, Pritchard S, Phillips G, Chan KW. Thalidomide in the management of chronic graft-versus-host disease in children following bone marrow transplantation. *Bone Marrow Transplant.* 1994;14(6):937-942.

44. Mehta P, Kedar A, Graham-Pole J, Skoda-Smith S, Wingard JR. Thalidomide in children undergoing bone marrow transplantation: series at a single institution and review of the literature. *Pediatrics.* 1999;103(4):e44.

45. Arora M WJ, Davies SM, Blazar BR, Defor T, Enright H, Miller WJ, Weisdorf DF. Randomized clinical trial of thalidomide, cyclosporine, and prednisone versus cyclosporine and prednisone as initial therapy for chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2001;7(5):265-273.

46. Koc S LW, Flowers ME, Anasetti C, Deeg HJ, Nash RA, Sanders JE, Witherspoon RP, Appelbaum FR, Storb R, Martin PJ. Thalidomide for treatment of patients with chronic graft-versus-host disease. *Blood.* 2000;96(12):3995-3996.

47. Chao NJ, Parker PM, Niland JC, et al. Paradoxical effect of thalidomide prophylaxis on chronic graft-vs.-host disease. *Biol Blood Marrow Transplant.* 1996;2(2):86-92.

48. Parker PM CN, Nademanee A, O'Donnell MR, Schmidt GM, Snyder DS, Stein AS, Smith EP, Molina A, Stepan DE, Kashyap A, Planas I, Spielberger R, Somlo G, Margolin K, Zwingenberger K, Wilsman K, Negrin RS, Long GD, Niland JC, Blume KG, Forman SJ. Thalidomide as salvage therapy for chronic graft-versus-host disease. *Blood.* 1995;86(9):3604-3609.

49. Kulkarni S PR, Sirohi B, Treleaven J, Saso R, Horton C, Atra A, Ortin M, Rudin C, Goyal S, Sankpal S, Meller S, Pinkerton CR, Mehta J, Singhal S. Thalidomide after allogeneic haematopoietic stem cell transplantation: activity in chronic but not in acute graft-versus-host disease. *Bone Marrow Transplant.* 2003;32(2):165-170.

50. Payvandi F, Wu L, Haley M, et al. Immunomodulatory drugs inhibit expression of cyclooxygenase-2 from TNF-alpha, IL-1beta, and LPS-stimulated human PBMC in a partially IL-10-dependent manner. *Cell Immunol.* 2004;230(2):81-88.

51. Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J Immunol.* 1999;163(1):380-386.

52. Dredge K, Marriott JB, Todryk SM, et al. Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity. *J Immunol.* 2002;168(10):4914-4919.

53. Schafer PH, Gandhi AK, Loveland MA, et al. Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. *J Pharmacol Exp Ther.* 2003;305(3):1222-1232.

54. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol.* 2004;22(16):3269-3276.

55. Galustian C, Klaschka DC, Meyer B, Labarthe M-C, Bartlett JB, Dalgleish AG. Lenalidomide (Revlimid(R), CC-5013) and ActimidTM (CC-4047) inhibit the function and expansion of T regulatory (Treg) cells in vitro: Implications for anti-tumor activity in vivo. *AACR Meeting Abstracts.* 2006;2006(1):1147-a-.

56. Verhelle D, Corral LG, Wong K, et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. *Cancer Res.* 2007;67(2):746-755.

57. Suppiah R, Srkalovic JG, Hussein MA. Immunomodulatory analogues of thalidomide in the treatment of multiple myeloma. *Clin Lymphoma Myeloma.* 2006;6(4):301-305.

58. Ito T, Ando H, Suzuki T, et al. Identification of a primary target of thalidomide teratogenicity. *Science.* 2010;327(5971):1345-1350.

59. Zhu YX, Braggio E, Shi CX, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. *Blood.* 2011;118(18):4771-4779.

60. Brustle A, Heink S, Huber M, et al. The development of inflammatory T(H)-17 cells requires interferon-regulatory factor 4. *Nat Immunol.* 2007;8(9):958-966.

61. Mudter J, Yu J, Zufferey C, et al. IRF4 regulates IL-17A promoter activity and controls RORgammat-dependent Th17 colitis in vivo. *Inflamm Bowel Dis.* 2011;17(6):1343-1358.

62. Bartlett JB DK, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer.* 2004;4(4):314-322.

63. Xu W CM, Sankar S, Webb DR, Bennett BL. CC-4047 promotes Th1 cell differentiation and reprograms polarized human Th2 cells by enhancing transcription factor T-bet. *Clin Immunol.* 2008;128(3):392-399.

64. Streetly MJ GK, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. *Br J Haematol.* 2008;141(1):41-51.

65. Schey SA FP, Bartlett JB, Clarke IA, Ashan G, Knight RD, Streetly M, Dalgleish AG. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol.* 2004;22(16):3269-3276.

66. Rusten LS JS. Tumor necrosis factor (TNF)-alpha directly inhibits human erythropoiesis in vitro: role of p55 and p75 TNF receptors. *Blood.* 1995;154(8):3732-3741.

67. Pusic I, DiPersio JF, Goran SL, et al. Pomalidomide (POM) In Advanced Corticosteroid-Resistant Chronic Graft-Versus-Host Disease (cGVHD). *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation.* 2010;16(2):S311.

68. Mesa RA PA, Hussein K, Wu W, Schwager S, Litzow MR, Hogan WJ, Tefferi A. Phase1/-2 study of Pomalidomide in myelofibrosis. *Am J Hematol.* 2010 Feb;85(2):129-130.

69. Lacy MQ HS, Gertz MA, Dispenzieri A, Buadi F, Kumar S, Greipp PR, Lust JA, Russell SJ, Dingli D, Kyle RA, Fonseca R, Bergsagel PL, Roy V, Mikhael JR, Stewart AK, Laumann K, Allred JB, Mandrekar SJ, Rajkumar SV. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *J Clin Oncol.* 2009;27(30):5008-5014.

70. Begna KH MR, Pardanani A, Hogan WJ, Litzow MR, McClure RF, Tefferi A. A phase-2 trial of low-dose pomalidomide in myelofibrosis. *Leukemia.* 2011;25(2):301-304.

71. Arai S, Jagasia M, Storer B, et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH Consensus Criteria. *Blood.* 2011;118(15):4242-4249.

72. Kuzmina Z, Eder S, Bohm A, et al. Significantly worse survival of patients with NIH-defined chronic graft-versus-host disease and thrombocytopenia or progressive onset type: results of a prospective study. *Leukemia.* 2011.

73. Mitchell SA, Jacobsohn D, Thormann Powers KE, et al. A multicenter pilot evaluation of the National Institutes of Health chronic graft-versus-host disease (cGVHD) therapeutic response measures: feasibility, interrater reliability, and minimum detectable change. *Biol Blood Marrow Transplant.* 2011;17(11):1619-1629.

74. Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol.* 2007;25(34):5490-5505.

75. Lee S, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2002;8(8):444-452.

13 APPENDICES

13.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.2 APPENDIX B: MEASUREMENT OF POMALIDOMIDE SERUM LEVELS

Blood and Plasma Sample Labeling

Labels must contain the following information:

- Protocol No.:
- Subject ID number:
- Nominal Time Point:

All blood and plasma collection tubes and storage vials should be labeled and chilled on wet ice **prior to** sample collection and processing.

Blood Sample Collection

- Research nurses will give the Figg lab 24 hours advance notice on PK blood draws.
- Fill an ice bucket with a sufficient amount of ice to pre-chill all collection tubes before blood draw.
- Collect approximately 6 mL of whole blood into a pre-chilled 6-mL K_3EDTA tube to which 1% hydrochloric acid has been added (supplied by Figg Laboratory). Blood can be collected via direct vein puncture or indwelling catheter.
- Accurately record the time of blood collection.
- Gently invert the tube 3-5 times and immerse it into ice immediately to prevent possible compound degradation at room temperature.
- The date, cycle day, and **exact** time of each blood draw should be recorded on the sample tube and the PK sheet containing the study number and unique patient identifier.
- Please page 102-11964 (Gareth Peters or alternate tech) for immediate pick-up. (Contact the Clinical Pharmacology Program (CPP) processing group in 10/5A09 at 301-594-6131 or 301-402-3622 with any questions).

Blood Sample Processing to Obtain Plasma

- Within 30 minutes of collection, the blood sample must be centrifuged at 1,500 g (about 3,000 rpm dependent upon the type of centrifuge) for 10 min at 4°C to obtain plasma.
- Using Eppendorf pipettes (or equivalent) to transfer approximately 0.7 mL of plasma into each of the two pre-labeled, pre-chilled, citric acid-containing polypropylene storage vials (one primary and one back-up, provide by Celgene). Keep storage vials on ice before they are ready to be transferred into a freezer.
- Within 60 minutes of blood collection, transfer plasma samples in storage vials into a –80ºC freezer, where they will remain stored until analysis.

- Immediately record the time of sample entry into the freezer.
- Patient data will be entered into a secure and encrypted LabSamples database maintained by the Clinical Pharmacology Program, Office of the Clinical Director

13.3 APPENDIX C: DIAGNOSTIC CRITERIA OF CHRONIC GVHD

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Skin	Poilkiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerosus-like features	Depigmentation	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting, or brittle features Onycholysis Pterygium unguis Nail loss [5,6]		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia[7] Scaling, papulosquamous lesion	Thinning scalp hair, typically patchy, coarse, or dull [8] Premature grey hair	

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Mouth	Lichen-type features Hyperkeratotic plaques Restriction of mouth opening from sclerosis	Xerostomia Mucocele Mucosal atrophy Pseudomembranes [6] Ulcers[6]		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes [9] Cicatricial conjunctivitis Keratoconjunctivitis sicca [9] Confluent areas of punctuate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis [10]	
Genitalia	Lichen planus-like features Vaginal scarring or stenosis	Erosions [6] Fissures [6] Ulcers [6]		
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs [12] and radiology [9]		BOOP [13]
Muscle, Fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis	Edema Muscle cramps Arthralgia or arthritis	

Organ or Site	Diagnostic Features[1]	Distinctive Features[2]	Others[3]	Common Features[4]
Hematopoietic and immune				Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hypergammaglobilinemia Autoantibodies (AIHA and ITP) [14]
Other				Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy

1.Sufficient to establish the diagnosis of cGvHD

2.Seen in cGvHD, but insufficient alone to establish a diagnosis of cGvHD

3.Can be acknowledged as part of the cGvHD symptomatology if the diagnosis is confirmed

4.Seen with both acute and cGvHD

5.Usually symmetric, affects most nails

6.In all cases, infection, drug effects, malignancy, or other causes must be excluded.

7.After recovery from chemoradiation therapy

8.Not explained by endocrine or other causes

9.Diagnosis of cGvHD requires biopsy or radiology confirmation (or Schirmer test for eyes)

10.Erythema of the eyelids with edema

11.Infants and children

12.Pulmonary function tests

13.Bronchiolitis obliterans-organizing pneumonia

14.AIHA: autoimmune hemolytic anemia; ITP: idiopathic thrombocytopenic purpura

13.4 APPENDIX D: CLINICAL DIFFERENTIATION OF ACUTE AND CHRONIC GVHD

Category	Time of Symptoms After HCT or DLI	Presence of Acute GVHD Features	Presence of Chronic GVHD Features[2]
Acute GVHD			
Classic acute GVHD	≤ 100 days	Yes	No
Persistent, recurrent, or late-onset acute GVHD	> 100 days	Yes	No
Chronic GVHD			
Classic cGvHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

1. Abbreviations: HCT: hematopoietic cell transplantation; DLI: donor lymphocyte infusion
2. See Appendix C for features

13.5 APPENDIX E: ORGAN SPECIFIC AND GLOBAL SCORING OF CHRONIC GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN *Clinical features:* ☐ Maculopapular rash ☐ Lichen planus-like features ☐ Papulosquamous lesions or ichthyosis ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Keratosis pilaris ☐ Erythema ☐ Erythroderma ☐ Poikiloderma ☐ Sclerotic features ☐ Pruritus ☐ Hair involvement ☐ Nail involvement **% BSA involved** ☐	☐ No Symptoms	☐ <18% BSA with disease signs but **NO** sclerotic features	☐ 19-50% BSA **OR** involvement with superficial sclerotic features "not hidebound" (able to pinch)	☐ >50% BSA **OR** deep sclerotic features "hidebound" (unable to pinch) **OR** impaired mobility, ulceration or severe pruritus
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

LIP Print Name:_____ **LIP Signature:**_____

Date of Evaluation:_____

Timepoint: Baseline_____ Off Study_____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
GI TRACT	☐ No symptoms	☐ Symptoms such as dysphagia, anorexia, nausea, vomiting, abdominal pain or diarrhea without significant weight loss (<5%)	☐ Symptoms associated with mild to moderate weight loss (5-15%)	☐ Symptoms associated with significant weight loss >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation
LIVER	☐ Normal LFT	☐ Elevated Bilirubin, AP*, AST or ALT <2 x ULN	☐ Bilirubin >3 mg/dl or Bilirubin, enzymes 2-5 x ULN	☐ Bilirubin or enzymes > 5 x ULN
LUNGS*	☐ 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 0_2)
FEV1 ☐	☐ FEV1 > 80% **OR** LFS=2	☐ FEV1 60-79% **OR** LFS 3-5	☐ FEV1 40-59% **OR** LFS 6-9	☐ FEV1 ≤39% **OR** LFS 10-12
DLCO ☐				
EYES Mean tear test (mm): ☐ >10 ☐ 6-10 ☐ ≤5 ☐ Not done	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requiring eyedrops ≤ 3 x per day) **OR** asymptomatic signs of keratoconjunctivitis sicca	☐ Moderate dry eye symptoms partially affecting ADL (requiring drops > 3 x per day or punctal plugs), **WITHOUT** vision impairment	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision caused by keratoconjunctivitis sicca

LIP Print Name:_____ **LIP Signature:**_____

Date of Evaluation:_____
Timepoint: Baseline _____ Off Study _____

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema 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.)
GENITAL TRACT	☐ No symptoms	☐ Symptomatic with mild signs on exam **AND** no effect on coitus and minimal discomfort with gynecologic exam	☐ Symptomatic with moderate signs on exam **AND** with mild dyspareunia or discomfort with gynecologic exam	☐ Symptomatic **WITH** advanced signs (stricture, labial agglutination or severe ulceration) **AND** severe pain with coitus or inability to insert vaginal speculum

* AP may be elevated in growing children, and not reflective of liver dysfunction

Other indicators, clinical manifestations or complications related to cGVHD (check all that apply and assign a score to its severity (0-3) based on its functional impact (none – 0,mild -1, moderate -2, severe – 3)

- ☐ Esophageal stricture or web___
- ☐ Pericardial Effusion___
- ☐ Pleural Effusion(s)___
- ☐ Ascites (serositis)___
- ☐ Nephrotic syndrome___
- ☐ Peripheral Neuropathy___
- ☐ Myasthenia Gravis___
- ☐ Cardiomyopathy___
- ☐ Eosinophilia > 500µl___
- ☐ Polymyositis___
- ☐ Cardiac conduction defects___
- ☐ Coronary artery involvement___
- ☐ Platelets <100,000/µl ___
- ☐ Progressive onset
- ☐ **OTHERS:** _____

LIP Print Name:_____ **LIP Signature:**_____

Date of Evaluation:_____

Timepoint: Baseline_____ Off Study_____

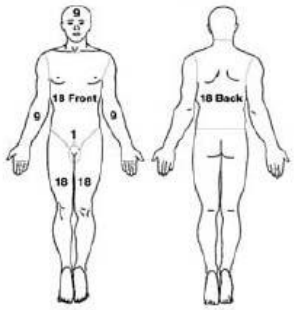
When discrepancy exists between pulmonary symptom or PFT scores the higher value should be used for final scoring. Scoring using the Lung Function Score (LFS) is preferred, but if DLCO is not available, grading using FEV1 should be used. The percent predicted FEV1 and DLCO (adjusted for hematocrit but not alveolar volume) should be converted to a numeric score as follows: >80% = 1; 70-79% = 2; 60-69% = 3; 50-59% = 4; 40-49% = 5; <40% = 6. The LFS = FEV1 score + DLCO score, with a possible range of 2-12.

13.6 APPENDIX F: GLOBAL SCORING OF CGVHD

Stage	Definition
Mild	Only 1 or 2 organs or site (except the lung) No clinically significant functional impairment (maximum of score 1 in all affected organs or sites)
Moderate	At least 1 organ or site with clinically significant but no major disability (maximum score of 2 in any affected organ or site), or 3 or more organs or sites with no clinically significant functional impairment (maximum score of 1 in all affected organs or sites)
Severe	Major disability caused by cGvHD (score of 3 in any organ or site) Lung function score ≥ 2

13.7 APPENDIX G: CHRONIC GVHD ASSESSMENT (CLINICIAN) FORM

Current Patient Weight: _____ Today's Date: _____ MR#/Name: ____

Component	**Findings**	**Scoring (see skin score worksheet)**
Skin 	Erythematous rash of any sort	% BSA (max 100%)
	Moveable sclerosis	% BSA (max 100%)
	Non-moveable sclerosis (hidebound/non-pinchable) or subcutaneous sclerosis/fasciitis	% BSA (max 100%)
	Ulcer(s): select the largest ulcerative lesion, and measure its longest dimension in cm and mark location of ulcer	Location: _____ Longest dimension: _____cm
Eyes Bilateral Schirmer's Tear Test (without anesthesia) in persons 9 years or older	Right Eye: mm of wetting	Left Eye: mm of wetting

Mouth	**Mucosal change**	No evidence of CGVHD		Mild		Moderate		Severe	
	Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3

Lichenoid	None	0	Hyperkeratotic changes(<25%)	1	Hyperkeratotic changes(25-50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
Mucoceles*	None	0	1-5 mucoceles	1	6-10 scattered mucoceles	2	Over 10 mucoceles	3
			*Mucoceles scored for lower labial and soft palate only				**Total score for all mucosal changes**	

Blood Counts	Platelet Count (K/uL)	ULN (K/uL)	Total WBC (K/uL)	ULN (K/uL)	Eosinophils (%)

Liver Function Tests	Total serum bilirubin (mg/dL)	ULN (mg/dL)	ALT (U/L)	ULN (U/L)	Alkaline Phosphatase (U/L)	ULN (U/L)

Gastrointestinal-Upper GI • Early satiety OR • Anorexia OR	*0= no symptoms* *1=mild, occasional symptoms, with little reduction in oral intake during the past week* *2=moderate, intermittent symptoms, with some reduction in oral intake during the past week*

• Nausea & Vomiting	*3=more severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the past week*		
Gastrointestinal-Esophageal • Dysphagia OR • Odynophagia	*0= no esophageal symptoms* *1=Occasional dysphagia or odynophagia with solid food or pills during the past week* *2=Intermittent dysphagia or odynophagia with solid foods or pills, but not for liquids or soft foods, during the past week* *3=Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week*		
Gastrointestinal-Lower GI • Diarrhea	*0= no loose or liquid stools during the past week* *1= occasional loose or liquid stools, on some days during the past week* *2=intermittent loose or liquid stools throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion* *3=voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion*		
Lungs • Bronchiolitis Obliterans	Pulmonary Function Tests with Diffusing Capacity (attach report for person> 5 yrs old)	FEV-1 (% Predicted)	Single Breath DLCO (adjusted for hemoglobin) (%Predicted)
Health Care Provider Global Ratings: **In your opinion, do you think that this patient's cGvHD is mild, moderate or severe?** 0=none	**Where would you rate the severity of this patient's cGvHD symptoms on the following scale, where 0 is CGVHD symptoms that are not at all severe and 10 is the most severe CGVHD symptoms possible:** 0 1 2 3 4 5 6 7 8 9 10 **cGvHD symptoms not at all severe** **cGvHD symptoms most severe**		**Over the past month would you say that this patient's CGVHD is** +3= Very much better +2= Moderately better +1= A little better 0= About the same

1= mild 2=moderate 3=severe		**possible**	-1=A little worse -2=Moderately worse -3=Very much worse
Karnofsky Performance	**Score**	**Performance Status Scale Definitions (Use Lansky Play Performance for persons < 16 years old)**	
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 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	

13.8 APPENDIX H: CALCULATIONS FOR PARTIAL RESPONSE IN CHRONIC GVHD

Organ and Starting Score or Value at Baseline	Partial Response Criterion[1]
Skin (% of BSA)	
> 50	e/s ≤ 0.5 and e > 0
25-50	s – e ≥ 25 and e > 0
< 25	Only CR; no PR possible
Eye (mm Schirmer's test)	
< 5 mm	e – s ≥ 5 mm and e < LLN
5-10 mm	Only CR; no PR possible
Mouth (Schubert Scale 0-15)	
> 8	e/s ≤ 0.5 and e > 0
4 – 7	s – e ≥ 4 and e > 0
< 4	Only CR; no PR possible
Hematology	
Platelet count	e – s ≥ 100,000/μL and e < LLN
Eosinophil count	
≥ 3 X ULN	e/s ≤ 0.5 and e > ULN
< 3 X ULN	Only CR; no PR possible
Gastrointestinal (0 -3 scales)	
3	e = 1 or 2
2	e = 1
1	Only CR; no PR possible
Liver function	
(ALT, alkaline phosphatase and bilirubin)	
≥ 3 X ULN	e/s ≤ 0.5 and e > ULN
< 3 X ULN	Only CR; no PR possible

Abbreviations: s: starting score or value; e: ending score or value; ULN: upper limit of normal; LLN: lower limit of normal

13.9 APPENDIX I: CALCULATIONS FOR PROGRESSION IN CHRONIC GVHD

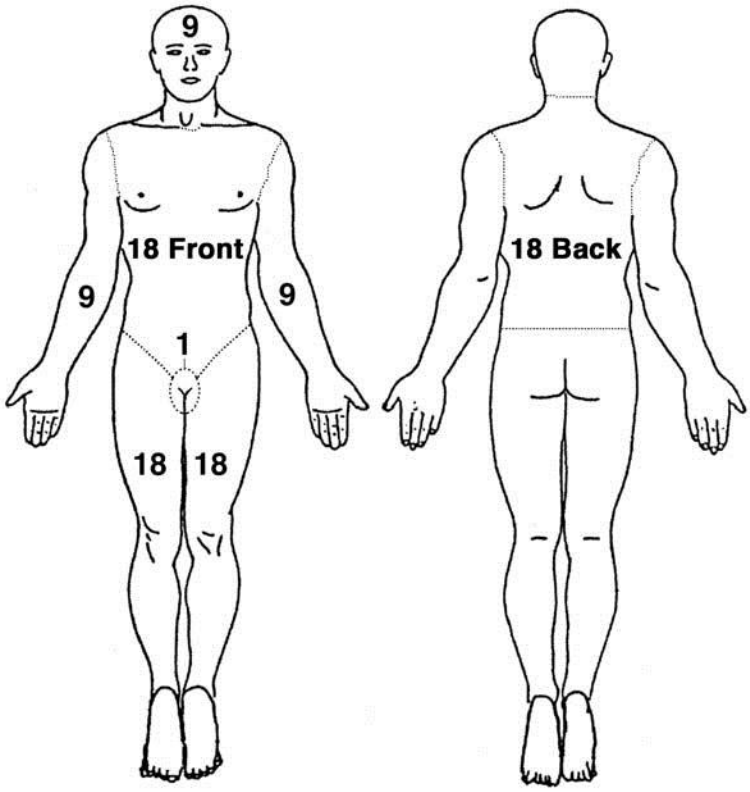
Organ and Starting Score or Value	Progression Criterion[1]
Skin (% of BSA)	e – s ≥ 25
Eye (mm Schirmer's test)	s – e ≥ 5 mm
Mouth (Schubert Scale 0-15)	e – s ≥ 3
Hematology Platelet count Eosinophil count ≥ 3 X ULN < 3 X ULN	 s – e ≥ 50,000/μL and e < LLN e - s ≥ 3 X ULN e - s ≥ 2 X ULN
Gastrointestinal (0 -3 scales)	e – s ≥ 1
Liver function (ALT, alkaline phosphatase and bilirubin) s ≥ 3 X ULN s < 3 X ULN	 e - s ≥ 3 X ULN e - s ≥ 2 X ULN
Lungs (Lung function scale 12 points)[2]	e - s ≥ 3

1. Abbreviations: starting score or value; e: ending score or value; ULN: upper limit of normal; LLN: lower limit of normal

2. If the starting lung function score is ≥ 10, progression is defined as ≥ 5% decrease of FEV1 in two tests measured at least 2 weeks apart.

13.10 APPENDIX J: CHRONIC GVHD CUTANEOUS ASSESSMENT WORKSHEET (ADULT)

	Erythematous changes			Moveable-sclerosis/Dermal sclerosis			Non-moveable/subcutaneous sclerosis or fasciitis		
	% region involved	Multiplier	Total BSA	% region involved	Multiplier	Total BSA	% region involved	Multiplier	Total BSA
Head/neck/scalp		0.09			0.09			0.09	
Anterior torso		0.18			0.18			0.18	
Posterior torso		0.18			0.18			0.18	
L. upper extrem.		0.09			0.09			0.09	
R. upper extrem.		0.09			0.09			0.09	
L. lower extrem. (incl. L. buttock)		0.18			0.18			0.18	
R. lower extrem. (incl. R. buttock)		0.18			0.18			0.18	
Genitalia		0.01			0.01			0.01	



Total Erythema ☐ **Total Dermal** ☐ **Total Subcut** ☐

_____ _____ _____

Signature Printed Name Date/Time

13.11 APPENDIX K: LEE SYMPTOM SCALE

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
a. Abnormal skin color	0	1	2	3	4
b. Rashes	0	1	2	3	4
c. Thickened skin	0	1	2	3	4
d. Sores on skin	0	1	2	3	4
e. Itchy skin	0	1	2	3	4
EYES AND MOUTH:					
f. Dry eyes	0	1	2	3	4
g. Need to use eyedrops frequently	0	1	2	3	4
h. Difficulty seeing clearly	0	1	2	3	4
i. Need to avoid certain foods due to mouth pain	0	1	2	3	4
j. Ulcers in mouth	0	1	2	3	4
k. Receiving nutrition from an intravenous line or feeding tube	0	1	2	3	4
BREATHING:					
l. Frequent cough	0	1	2	3	4
m. Colored sputum	0	1	2	3	4
n. Shortness of breath with exercise	0	1	2	3	4
o. Shortness of breath at rest	0	1	2	3	4
p. Need to use oxygen	0	1	2	3	4
EATING AND DIGESTION:					

	Not at all	Slightly	Moderately	Quite a bit	Extremely
q. Difficulty swallowing solid foods	0	1	2	3	4
r. Difficulty swallowing liquids	0	1	2	3	4
s. Vomiting	0	1	2	3	4
t. Weight loss	0	1	2	3	4
MUSCLES AND JOINTS:					
u. Joint and muscle aches	0	1	2	3	4
v. Limited joint movement	0	1	2	3	4
w. Muscle cramps	0	1	2	3	4
x. Weak muscles	0	1	2	3	4
ENERGY:					
y. Loss of energy	0	1	2	3	4
z. Need to sleep more/take naps	0	1	2	3	4
aa. Fevers	0	1	2	3	4
MENTAL AND EMOTIONAL:					
bb. Depression	0	1	2	3	4
cc. Anxiety	0	1	2	3	4
dd. Difficulty sleeping	0	1	2	3	4

13.12 APPENDIX L: POMALIDOMIDE PREGNANCY PREVENTION RISK MANAGEMENT PLANS

This Appendix applies to all patients receiving pomalidomide therapy. The following Pregnancy Risk Minimization Plan documents are included in this Appendix:

1) Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Appendix M);
2) Pomalidomide Information Sheet (Appendix N).

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Appendix M) provides the following information:
    - Potential risks to the fetus associated with pomalidomide exposure
    - Definition of Female of Childbearing Potential (FCBP)
    - Pregnancy testing requirements for patients receiving Pomalidomide who are females of childbearing potential
    - Acceptable birth control methods for both female of childbearing potential and male patients receiving pomalidomide in the study
    - Requirements for counselling of all study patients receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
2. The Pomalidomide Information Sheet (Appendix N) will be given to each patient receiving pomalidomide study therapy. The patient must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

13.13 APPENDIX M: POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who is menstruating, amenorrheic from previous medical treatments, under 50 years of age and/or perimenopausal and do not qualify for the females not of reproductive potential category.

Criteria for females not of reproductive potential:

Defined as females who have been in natural menopause for at least 24 consecutive months, or who have had a hysterectomy and/or bilateral oophorectomy.

Counselling

For a female of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section **2.2**)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male patients taking pomalidomide must meet the following conditions (ie, all males must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

<u>Contraception</u>

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Because of the increased risk of venous thromboembolism in patients taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after

discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counselling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counselling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counselling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

13.14 APPENDIX N: POMALIDOMIDE INFORMATION SHEET

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits. **If you are a female who is able to become pregnant:**

- **Do not take study drug if you are pregnant or plan to become pregnant**
- **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
  - for 28 days before starting study drug
  - while taking study drug
  - during dose interruptions of study drug
  - for 28 days after stopping study drug
- **You must have pregnancy testing done at the following times:**
  - within 10 – 14 days and again 24 hours prior to the first dose of study drug
  - weekly for the first 28 days
  - every 28 days after the first month or every 14 days if you have irregular menstrual periods
  - if you miss your period or have unusual menstrual bleeding
  - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
  - at discontinuation of study drug
- **Stop taking study drug if you become pregnant during treatment**
  - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.
- **Do not breastfeed while taking study drug**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

1. Male patients (including those who have had a vasectomy) must either **not have any sexual relations with a pregnant female or a female who can become pregnant,** or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
   - While you are taking study drug
   - During dose interruptions of study drug
   - For 28 days after you stop taking study drug
2. **Male patients should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
3. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
   1. **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
   2. **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
   3. **Do not break, chew, or open study drug capsules.**
   4. You will be supplied with no more than one cycle of study drug
   5. Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

13.15 APPENDIX O: MEDICATION DIARY

Today's date _____

Patient Name_____ Patient Study ID_____**INSTRUCTIONS TO THE PATIENT:**

1. Complete one form for each cycle.
2. You will take your dose of pomalidomide each day at approximately the same time. Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Caregivers who are women able to become pregnant should not handle pomalidomide unless wearing gloves. You will take ____0.5 mg capsules, ____1 mg capsules and ____ 2 mg capsules each day.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	**Day**	**Time of daily dose**	**# of capsules taken**			**Comments**
			0.5 mg	**1 mg**	**2 mg**	
	1					
	2					
	3					
	4					
	5					
	6					
	7					
	8					
	9					
	10					
	11					
	12					
	13					
	14					

Patient Name_____ Patient Study ID_____

(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle.
2. You will take your dose of pomalidomide each day at approximately the same time. Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Caregivers who are women able to become pregnant should not handle pomalidomide unless wearing gloves. You will take ____0.5 mg capsules, ____1 mg capsules and ____ 2 mg capsules each day.
3. Record the date, the number of capsules of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	**Day**	**Time of daily dose**	**# of capsules taken**			**Comments**
			0.5 mg	**1 mg**	**2 mg**	
	15					
	16					
	17					
	18					
	19					
	20					
	21					
	22					
	23					
	24					
	25					
	26					
	27					
	28					

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____ Date patient was removed from study _____
2. Patient's planned daily dose_____ Total number of pills taken this month _____

Physician/Nurse/Data Manager's Signature _____

13.16 APPENDIX P: DATA COLLECTION ELEMENTS REQUIRED BY PROTOCOL

ALL OF THE FOLLOWING ELEMENTS WILL BE RECORDED IN THE C3D DATABASE.

A. PATIENT ENROLLMENT

Recipient

- Date of birth, age, gender, race, ethnicity
- Height
- Weight
- Karnofsky Performance Status
- Date of original diagnosis of the underlying disease (month/year)
- Diagnosis for which transplant was performed
- Date and type of transplant
- Conditioning regimen
- Acute GVHD yes/no
- Chronic GVHD date of diagnosis
- Chronic GVHD classification (late, overlap, classic)
- Prior systemic therapy for cGVHD
- Prior therapy for cGVHD
- Date of Informed Consent signature, consent version and date of registration
- Baseline History/Physical
- Baseline Symptoms
- Intensity of current immunosupression: None, Mild (single agent prednisone $\leq$0.5 mg/kg/day), Moderate (prednisone $\geq$0.5 mg/kg/day and or any single agent/modality), High (2 or more agents/modalities $\pm$prednisone $\geq$0.5 mg/kg/day)
- Clinician's impression of activity: Inactive, off systemic therapy or topical immunosupression; Inactive, on systemic therapy or topical immunosupression; Active, irrespective of the level of current therapy; Highly Active, irrespective of the level of current therapy
- Findings of consultations done at screening

Donor

- Age at transplant
- Relationship, gender
- Degree and type of HLA match (allele or serologic)
- CMV status

B. STUDY DRUG ADMINISTRATION AND RESPONSE FOR EACH COURSE OF THERAPY GIVEN

- Dates study drug given
- Actual dose given
- Response assessment

C. LABORATORY AND DIAGNOSTIC TEST DATA

- All Clinical laboratory and diagnostic test results done at screening except diagnostic tests which are not specified in the protocol, and if the results are not needed to document the start or end of an adverse event that requires reporting.
- All tests done to document resolution of adverse events
- Serologies-CMV and HSV

D. ADVERSE EVENTS

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

E. CONCOMITANT MEASURES

- Baseline immunosuppresive medications
- Other therapy for recorded adverse events

F. Off study

- Date and reason for off study
- Date and cause of death
- Autopsy findings

13.17 APPENDIX Q:CHRONIC GVHD COMPOSITE ASSESSMENT SCALE – EVALUATION TOOLS

13.17.1 Component 1: Skin

Patient Name: _____ Patient MR #: _____

Date of Assessment: _____

1. CAS - Initial assessment

    a. Extent (% body surface area, BSA) of involvement are estimated for lichenoid, sclerotic, and fascial disease.

    b. A score 0-3 (none, mild, moderate, severe) are given that directly correlates with BSA affected (see table below)

    c. The highest score in any skin sub-type are used to determine the overall stage of involvement

- **Check appropriate box in each row**

Sub-type	**Normal=0**		**MILD=1**		**MODERATE=2**		**SEVERE=3**	
Erythema / Lichenoid	0		1-25% BSA		25 – 50%BSA		3 = > 50% BSA	
Sclerosis, movable	0		1-25% BSA		25 – 50%BSA		3 = > 50% BSA	
Sclerosis, fixed (fasciitis)	0		1-25% BSA		25 – 50%BSA		3 = > 50% BSA	

Overall stage (max 3): ____

_____ _____ _____
Signature Printed Name Date/Time

2. Not in CAS - Objective ancillary data (presence or absence)

Pigment alteration (%)		Erosions/ ulcerations		Nail dystrophy		Alopecia		Edema		Xerosis	
Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent

%

3. Not in CAS - Subjective assessments --- Patient Visual Analog Scales

Pain 0 10

Itching 0 10

10

Definitions: Pain due to skin disease from zero (no pain) to 10 (worst imaginable pain)
Itching is level of discomfort from itching from zero (no itching) to 10 (worst imaginable itching)
Clinical severity is patient's assessment of degree of disease activity on the skin

Pain (0-10)	Pruritus (0-10)	Clinical severity (0-10)	
		Patient	Physician

Date of bx	Clinical findings	Group received	Location of bx	Affected/ Unaffected	Bx reason (D, R, D/R)*

*D- Diagnostic; R-Research, D/R- Diagnostic/Research.

Signature Printed Name Date/Time

13.17.2 Component 2: Mouth

1. CAS – Initial assessment

- Please, check off the box.

Instrument	Clinical Sign or Symptom	Normal=0		Mild=1		Moderate=2		Severe=3	
Oral Mucositis Rating Scale (CAS)	Oral signs of cGVHD	0		1 to 34		35-69		70-103+	

OMRS Score:_____

Stage: _____

2. Biopsy of oral mucosa (please check off the box):

A. Research Biopsy (Dr. Hakim's lab) □ YES □NO Size(mm)____

B. Clinical Biopsy (Pathology) □ YES □NO Size(mm)____

C. Minor Salivary Gland □ YES □NO

3. Amount of saliva collected in 5 min: _____

Date: ____/____/____ LIP print name: _____

LIP_____ **Signature:** _____

Schubert Oral Mucositis Rating Scale

Date: ____/____/____ LIP print name:_____LIP_____
Signature: _____

INSTRUCTIONS: Assess each indicated oral cavity location for the stated clinical observation and write in the number corresponding to the rating.

	LIPS		LABIAL MUCOSA		BUCCAL MUCOSA	
	Lower	Upper	Lower	Upper	Right	Left
Atrophy						
Pseudomembrane						
Erythema						
Hyperkeratosis						
Lichenoid						
Ulceration						
Edema/Cellulitis						

	TONGUE			FLOOR OF MOUTH	PALATE		GINGIVA
	Dorsal	Lateral	Ventral		Hard	Soft	
Atrophy							
Pseudomembrane							
Erythema							
Hyperkeratosis							
Lichenoid							
Ulceration							
Edema/Cellulitis							

Total OMRS Score: _____ (range: 0 – 273; sum all items)

<u>Instructions for Rating</u>:

Atrophy, erythema, hyperkeratosis, lichenoid, and edema and Pseudomembrane
Change is rated from normal.
0 = Normal/No change
1 = Mild change
2 = Moderate change
3 = Severe change

Ulceration
0 = None
1 = > 0 but ≤ 1cm^2
2 = >1 cm^2 but ≤ 2 cm^2
3 = > 2cm^2

If any area cannot be assessed, circle one of the following:
04 = Unable to visualize/assess due to severity
05 = Unable to assess because patient is sedated
06 =Unable to assess because patient is disoriented
07 = Unable to assess because patient is comatose
08 = Unable to assess because patient is unwilling or unable to cooperate
09 = Unable to assess because patient is not available. Explain: _____
10 = Other. Explain: _____
99 = Missing

Check (√) type of light source used to visualize the oral cavity:
____ (1) Otoscope ___ (2) Dental Light _____ (3) Other _____

_____ (1) Oral water rinse used
_____ (2) Local anesthetic used

Notes: Patient asked to rate oral pain using the Painometer and to rate dryness verbally (0 = none to 10= worst):

Oral pain: _____
Pain on swallowing _____
Dryness in mouth _____
Dryness in throat: _____

Mouth Opening: _____ mm

Periodontal Screening:

Date: ___/___/___ LIP print name:_____LIP Signature:_____

Time: _____

Instrument	Variable Assessed	Mild Inflammation=0 .1-1.0	Moderate Inflammation=1 .1-2.0	Severe Inflammation= 2.1-3.0
Gingival Index (Harald Löe)	Qualitative change of the gingival soft tissues			

Instrument	Variable Assessed	Excellent Plaque Control=0	Good Plaque Control=0.1 -0.9	Fair Plaque Control=1.0 -1.9	Poor Plaque Control=2.0-3.0
Plaque Index (Silness and Löe)	The severity and location of the soft debris aggregates				

Instructions:

Gingival Index

Upon palpation of the gingiva and running a blunt instrument (periodontal probe) along the soft tissue wall of the entrance of the gingival crevice the gingiva is examined and categorized the following way:

GI=0: is the score given to the gingiva the color of which is pale pink to pink. The surface after drying is matt. The degree of stippling may vary. The gingival margin may be located on the enamel or at various levels apical to the cemento-enamel junction. Although the margin should be thin, the buccal and lingual gingiva may present a rounded termination against the tooth, thereby forming the entrance or orifice of the gingival crevice. The form of the interdental gingiva depends on the space and size of the interdental areas. The tip of the papilla should be the most incisally or occlusally located part of the gingiva. On palpation, the gingival should be firm.

GI=1: is the score given when the gingiva is subject to mild inflammation. The gingival margin is slightly more reddish or bluish-reddish than normal and there is slight edema of the margin. A colorless gingival exudate may be observed or collected at the entrance of the crevice. Bleeding is not provoked.

GI=2: This is the score for a moderately inflamed gingiva. The gingiva is red or reddish-blue and glazy. There is enlargement of the margin due to edema. Bleeding is provoked.

GI=3: is the score for severe inflammation. The gingiva is markedly red or reddish-blue and enlarged. There is a tendency to spontaneous bleeding. Ulceration may be seen.

Plaque Index

PI=0: This score is given when the gingival area of the tooth surface is literally free of plaque. The surface is tested by running a pointed probe across the tooth surface at the entrance of the gingival crevice after the tooth has been properly dried, and if no soft matter adheres to the point of the probe, the area is considered clean.

PI=1: This score is given when no plaque can be observed in situ by the unarmed eye, but when the plaque is made visible on the point of the probe after this has been moved across the tooth surface at the entrance of the gingival crevice.

PI=2: This score is given when the gingival area is covered with a thin to moderately thick layer of plaque. The deposit is visible to the naked eye.
PI=3: Heavy accumulation of soft matter, the thickness of which fills out the niche produced by the gingival margin and the tooth surface. The interdental area is stuffed with soft debris.
Scoring For both indices, scores are given for distal, buccal, mesial and lingual surfaces. The scores are added together and divided by the number of surfaces scored (4), and then divided by the number of teeth scored (6). This is your Gingival Index or Plaque Index score.

VISUAL ANALOG SCALE FOR XEROSTOMIA

1. Rate the difficulty you experience in speaking due to dryness.

_____

Not difficult at all — Very difficult

2. Rate the difficulty you experience in swallowing due to dryness.

_____

Not difficult at all — Very difficult

3. Rate the dryness of your mouth.

_____

Not dry at all — Very dry

SCORE: _____

Date: ____/____/____ **LIP print name:**_____**LIP Signature:**_____

NUMERIC RATING SCALES (0-10) FOR ORAL PAIN, SENSITIVITY, AND DRYNESS

ORAL PAIN/SENSITIVITY

On a 0 to 10 scale, how SENSITIVE or PAINFUL was your mouth at its WORST in the past month? Please circle the number.

0	1	2	3	4	5	6	7	8	9	10
No sensitivity sensitivity										Worst

ORAL DRYNESS

On a 0 to 10 scale, how DRY is your mouth at its WORST in the past month? Please circle the number.

0	1	2	3	4	5	6	7	8	9	10
No dryness										Worst dryness

Global Scale

Compared to one month ago, what is the overall condition of your mouth? Please circle.

Much worse *A little worse* *Same* *A little better* *Much better*

LIP Print Name:_____**LIP Signature:**_____

Date of Evaluation:_____

ORAL HEALTH IMPACT PROFILE (OHIP-14)

Date: ____/____/____ LIP print name:_____LIP Signature:_____

#	Because of problems with your teeth, denture or mouth have you..	Never (0)	Hardly ever (1)	Occasionally (2)	Often (3)	Very Often (4)
1	*Had trouble pronouncing words*					
2	*Felt sense of taste has worsened*					
3	*Had painful aching in the mouth*					
4	*Found it uncomfortable to eat any foods*					
5	*Have been self-conscious*					
6	*Felt tense*					
7	*Had an unsatisfactory diet*					
8	*Had to interrupt meals*					
9	*Found it difficult to relax*					
10	*Have been a bit embarrassed*					
11	*Have been irritable with other people*					
12	*Had difficulty doing usual jobs*					
13	*Felt life in general was less satisfying*					
14	*Have been totally unable to function*					

Total _____

13.17.3 Component 3: Vaginal/Vulvar

13.17.3.1 Vaginal/Vulvar-Initial assessment form

Note: patient won't be referred if less than 16

Patient Name: _____ Patient MR #: _____

Date of Assessment: _____

1. **CAS – Initial assessment**

Please, check all boxes that pertain

NORMAL=0		**MILD=1**		**MODERATE=2**		**SEVERE=3**	
Vulva OR Vagina		Vulva		Vulva		Severe Vulva OR Vagina	
No symptoms		Erythema around openings of vestibular glands OR		Erosions on flat surfaces most notable on vulva OR		Vulvar architectural changes such as nearly complete resorption of the labia minora and clitoral agglutination OR	
		Generalized erythema / edema of vulva including vestibule OR		Fissures in vulvar folds (e.g. interlabial sulci; fourchette) OR		Vaginal synechiae including shortened vagina OR	
		Periurethral or other patchy erythema OR		Increased friability of vulvar mucosa		Hematocolpos OR	

NORMAL=0		MILD=1		MODERATE=2		SEVERE=3	
		Leukokeratosis (r/o HPV)				Introital stenosis OR	
						Myofascial pain/spasm of levator or pelvic floor muscles	

Overall stage (determined by most severe finding): _____

2. **Not in CAS – Gynecologic history**

Reason for BMT::_____

Type of BMT:_____

Date(s) of BMT:_____

Current immunosuppressive medications:

_____

3. **Menstrual history:**

How old were you when you first had a period? _____

Were your periods regular before you had your BMT? Yes/No

Are you still getting periods? Yes/No

When was your last menstrual period? _____

Did your BMT or other treatment affect your periods? Yes/No

If yes, how? Less frequent/ More frequent/ Stopped

Describe_____

4. **Hormone use:**

Did you use hormones after your BMT? Yes/No

If yes, which ones (Check all that apply)

5. **Combined hormones**

Birth control pills: Yes / No Dates:_____

Prempro: Yes / No Dates:_____

Estradiol/prog (FemHRT) Yes / No Dates:_____

Estrodiol/test (Estratest) Yes / No Dates:_____

Other: _____ Dates: _____

6. **Menopausal hormones – estrogens:**

Estrogen oral pill: Yes/No Dates: _____

Estrogen topical cream: Yes/No Dates: _____

Estrogen vaginal pill: Yes/No Dates: _____

Estrogen patch: Yes/No Dates: _____

Estrogen ring: Yes/No Dates: _____

Other: _____ Dates: _____

7. **Menopausal hormones – progesterone:**

Progesterone: Yes/No Dates: _____

Provera: Yes/No Dates: _____

Other: _____ Dates: _____

Are you currently taking hormones? Yes/No

Specify _____

Any contraindications to hormone use? Yes/No

Specify _____

8. **Gynecologic surgery history:**

Have you ever had gynecology surgery? Yes/No

Specify what surgery and year _____

Do you still have a uterus? Yes/No

Do you still have your ovaries? Yes/No

9. **Pap smear history:**

Have you ever had an abnormal pap? Yes/No; if yes, when?_____

What was done? _____

When was your last pap smear? _____

Was it normal or abnormal? _____

10. **STD history:**

Have you ever been told you have had any of the following?

Chlamydia: Yes/No

Gonorrhea: Yes/No

Genital herpes: Yes/No

Warts or HPV: Yes/No

Dysplasia: Yes/No

11. Obstetric history:

Have you ever been pregnant? Yes/No How many times? _____

12. Sexual history:

Have you ever been sexually active? Yes/No

Are you sexually active currently? Yes/No

Have you had intercourse since your transplant? Yes/No

Describe _____

13. **Not in CAS - Questions addressing pain when the vulva is touched**

Do you have pain when nothing is touching the vulva? Yes/No

Do you have vulvar pain or burning when you urinate? Yes/No

If yes, is this when the urine touches the vulva? Yes/No

If yes, does the pain makes you want to urinate? Yes/No

Do you have vulvar pain or burning when you:

Insert a tampon: Yes/No/NA

Wear tight jeans or pants: Yes/No/NA

When you ride a bike: Yes/No/NA

During foreplay: Yes/No/NA

When the penis touches the vulva: Yes/No/NA

Does the vulvar pain prevent or interrupt intercourse? Yes/No/NA

Do you have pain with deep penetration of the penis? Yes/No/NA

Have you been told there is scarring in the vagina? Yes/No/NA

Do you think there is scarring in the vagina? Yes/No/unknown

_____	_____	_____
Signature	Printed Name	Date

13.17.3.2 Vaginal/Vulvar-follow-up form

1. **CAS – Initial assessment**

- Please check all boxes that pertain

NORMAL=0		MILD=1		MODERATE=2		SEVERE=3	
Vulva OR Vagina		Vulva		Vulva		Severe Vulva OR Vagina	
No symptoms		Erythema around openings of vestibular glands **OR**		Erosions on flat surfaces most notable on vulva **OR**		Vulvar architectural changes such as nearly complete resorption of the labia minora and clitoral agglutination OR	
		Generalized erythema / edema of vulva including vestibule **OR**		Fissures in vulvar folds (e.g. interlabial sulci; fourchette) **OR**		Vaginal synechiae including shortened vagina **OR**	
		Periurethral or other patchy erythema **OR**		Increased friability of vulvar mucosa		Hematocolpos **OR**	
		Leukokeratosis (r/o HPV)				Introital stenosis **OR**	
						Myofascial pain/spasm of levator or pelvic floor muscles	

Overall stage (determined by most severe finding): _____

2. Not in CAS – Gynecologic follow-up

History and Clinical course since last visit_____
_____
_____
_____

Current systemic immunosuppressive medications_____
_____
_____

- Have you used topical temovate on the vulva since your last visit? Yes / No

Describe use and effect _____
_____

- Have you used hormone therapy since your last visit? Yes / No

  Specify _____

Describe use and effect _____
_____

Pap smear:

- When was your last pap smear? _____
- Was it normal or abnormal? _____

Sexual history:

- Have you been sexually active since your last visit? Yes / No
- If yes, was it painful? Yes / No
- Did you have pain after intercourse? Yes / No
- If yes, How long did the pain last?_____

Any other comments:_____

_____

Do you have pain when nothing is touching the vulva? Yes / No/ NA

Do you have vulvar pain or burning when you urinate? Yes / No/ NA

If yes, is this when the urine touches the vulva? Yes / No/ NA

If yes, does the pain makes you want to urinate? Yes / No/ NA

Do you have vulvar pain or burning when you:

- Wear tight jeans or pants: Yes / No/ NA
- When you ride a bike: Yes / No/ NA
- During foreplay: Yes / No / NA
- When the penis touches the vulva: Yes / No/ NA

Since the last visit:

- Does the vulvar pain prevent or interrupt intercourse? Yes / No/ NA
- Do you have pain with deep penetration of the penis? Yes / No/ NA
- Have you been told there is scarring in the vagina? Yes / No/ NA
- Do you think there is scarring in the vagina? Yes / No/ unknown

RECOMMENDATIONS: _____

_____

_____	_____	_____
Signature	Printed Name	Date

13.17.4 Component 3: Function

Description

There are standard ranges for all tests. Every joint has an established range of motion (ROM). For example, the normal ROM for shoulder flexion is 180 degrees, each quartile is 45 degrees. If the shoulder can be put through 125 degrees it is 75% of normal. Similar is for grip strength (in Kg or pounds of pressure) and for walk time. The velocity is established based on norms for age and sex. For example if 18 feet/second, if divided by 4 and gets quartiles.

Patient Name: _____ Patient MR #: _____

Date of Assessment: _____

Assessed: Yes/No

Assessed Partially: Yes/No

Reason if "No": age restriction

1. CAS – Initial Assessment

- PLEASE ASSESS in according to age restrictions for each parameter
- Please, check off the appropriate box

	Musculoskeletal findings							
Parameter	**NORMAL=0**		**MILD=1**		**MODERATE=2**		**SEVERE=3**	
ROM* Assess if patient ≥ 4	0-25%		26-50%		51-75%		>75%	
grip strength* Assess if patient ≥ 6	0-25%		26-50%		51-75%		I. > 75%	
walk velocity* Assess if patient ≥ 6	0-25%		26-50%		51-75%		II. > 75%	
HAP* Assess if patient ≥ 16	>81		73-81		61-72		<61	

*** Reduction in maximal performance**

Overall stage (max3): _____

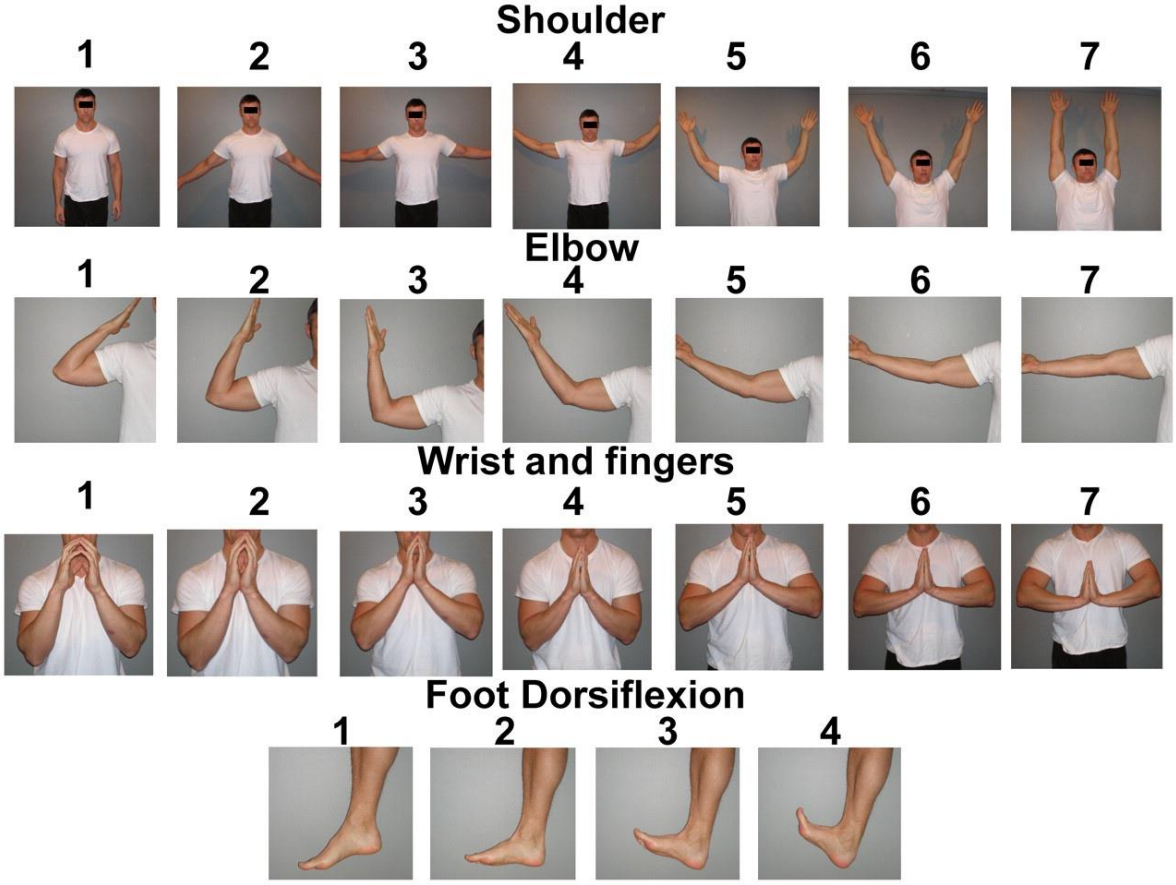
Total score (max 12): _____

Parameter	**Actual Number****					**% of predicted*****
ROM						
grip strength *Dominant Hand* *R L* *Circle One*		Trial 1	Trial 2	Trial 3	Average	
	Right					
	Left					
walk velocity	Total Distance Walked in 2 Minutes: _____ feet walked in 2 minutes _____ feet walked in 6 minutes					
HAP	MAS		AAS			

**** Please provide the actual result of reduction in maximal performance**
***** Please provide the actual result as % of predicted**

_____ _____ _____
Signature Printed Name Date

2. P-ROM


Shoulder
1
2
3
4
5
6
7
Elbow
1
2
3
4
5
6
7
Wrist and fingers
1
2
3
4
5
6
7
Foot Dorsiflexion
1
2
3
4

3. Occupational Therapy

1. CAS outcome measures:

Dx: _____

Date of transplant: _____

Date of evaluation:_____
Timepoint:_____

Instrumental Activities of Daily Living:

Frenchay Activities Index:_____

Activity Card Sort:_____

Basic Self Care:

Barthel Index:_____

Motor Function:

Disabilities of the Arm Hand and Shoulder (DASH) score :_____

Manual Abilities Measure: _____

Grooved Peg board

1. Total time dominant hand: _____seconds
2. Total time non dominant hand:_____seconds

Recommendations:

Date of Evaluation: _____LIP

Signature:_____/phone::301-451-7502

2. Manual Ability Measure (MAM-36)

Patient ID: _____ Today's Date: __ __ __ __ __

Age: _____ Gender: __ __ __ Highest Level of Education: _____

Race____ (White, African American, American Indian, Asian-Pacific, Mixed Races, Don't know)

Are you Hispanic? _____Yes, _____No

Are you currently employed? If so, what is your occupation Gob title)?

_____

If not, what was your occupation before you were diagnosed with your current condition?

_____

What is your diagnosis for coming to the clinic?_____ __

How long ago were you diagnosed with this condition?_____

_

Do you have any other medical problems that affect the use of your hands?

If you have had hand surgery, or if you have surgery scheduled, please indicate the date(s) and what was/will be done:

_____

Which is your dominant hand?
Right ____, Left ____, Ambidextrous ____, Don't know ____

Which hand(s) has limited function or hand use? Both__, Right __, Left ____,

Do you live alone now?
Yes No ___, with

INSTRUCTIONS:

Please circle one response regarding how easy or how hard it is for you to perform the following tasks.

Easy (4) =I can do the activity without any problem.

A little hard (3) = I usually do the task myself, although it takes longer or more effort now than before (i.e., before having current diagnosis/condition/disability). Sometimes, there is pain or discomfort when I do the task.

Very hard (2) = It is very hard for me to do the task and I usually ask others to do it for me unless no one is around.

Cannot do (1) =I am unable to do the task all by myself.

Almost Never do (0) =I have not done and almost will never do the task, even though I think I can do it.

Task	Easy	A little hard	Very hard	Cannot do	Never do
Eat a sandwich	4	3	2	1	0
Drink a glass of water	4	3	2	1	0
Pick up a half-full water pitcher	4	3	2	1	0
Use a spoon or fork	4	3	2	1	0
Butter bread (Put butter or jam on	4	3	2	1	0
Cut meat on a plate with a knife	4	3	2	1	0
Squeeze toothpaste	4	3	2	1	0
Brush teeth :	4	3	2	1	0
Brush or comb hair	4	3	2	1	0
Wash hands	4	3	2	1	0
Wring a towel '	4	3	2	1	0
Zip pants	4	3	2	1	0
Zip a jacket	4	3	2	1	0
Button clothes	4	3	2	1	0
Fasten a clothes snap or hook	4	3	2	1	0
Cut nails with a nail clipper	4	3	2	1	0
Tie shoes with laces	4	3	2	1	0

Task	Easy	A little hard	Very hard	Cannot do	Never do
Use a remote control	4	3	2	1	0
Key in telephone numbers	4	3	2	1	0
Turn door knob to open a door	4	3	2	1	0
Turn key to open a lock	4	3	2	1	0
Carry a shopping bag with a hand loop	4	3	2	1	0
Open a previously-opened wide-mouth jar (jam, pickle)	4	3	2	1	0
Open a previously-unopened carton box (milk, cereal)	4	3	2	1	0
Pour liquid from a bottle into a glass	4	3	2	1	0
Open a medicine bottle with child-proof top	4	3	2	1	0
Open an envelope without a letter Opener	4	3	2	1	0
Peel vegetables or fruits	4	3	2	1	0
Count money (bills and coins)	4	3	2	1	0
Take things out of a wallet (bills, papers, credit cards)	4	3	2	1	0
Write 3 to 4 sentences legibly	4	3	2	1	0
Tum pages of a book	4	3	2	1	0
Use a hammer or screwdriver	4	3	2	1	0
Fold clothes after laundering	4	3	2	1	0
Take a CD/DVD out of its case and put it onto a player/drive	4	3	2	1	0

3. Human Activity Profile

Instructions

- Please check each activity according to these directions:
- Check Column 1 ("Still Doing This Activity") if:
- You completed the activity unassisted the last time you had the need or opportunity to do so.
- Check Column 2 ("Have Stopped Doing This Activity") if:
- You have engaged in the activity in the past, but you probably would not perform the activity today even if the opportunity should arise.
- Check Column 3 ("Never Did This Activity") if:
- You have never engaged in the specific activity.

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
1. Getting in and out of chairs or bed (without assistance)			
2. Listening to the radio			
3. Reading books, magazines or newspapers			
4. Writing (letters, notes)			
5. Working at a desk or table			
6. Standing (for more than one minute)			
7. Standing (for more than five minutes)			
8. Dressing or undressing (without assistance)			
9. Getting clothes from drawers or closets			
10. Getting in or out of a car (without assistance)			
11. Dining at a restaurant			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
12. Playing cards/table games			
13. Taking a bath (no assistance needed)			
14. Putting on shoes, stockings or socks (no assistance needed)			
15. Attending a movie, play, church event or sports activity			
16. Walking 30 yards (27 meters)			
17. Walking 30 yards (non-stop)			
18. Dressing/undressing (no rest or break needed)			
19.Using public transportation or driving a car (100 miles or less)			
20. Using public transportation or driving a car (99 miles or more)			
21. Cooking your own meals			
22. Washing or drying dishes			
23. Putting groceries on shelves			
24. Ironing or folding clothes			
25. Dusting/polishing furniture or polishing cars			
26. Showering			
27. Climbing six steps			
28. Climbing six steps (non-stop)			
29. Climbing nine steps			
30. Climbing 12 steps			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
31. Walking ½ block on level ground			
32. Walking ½ block on level ground (non-stop)			
33. Making a bed (not changing sheets)			
34. Cleaning windows			
35. Kneeling, squatting to do light work			
36. Carrying a light load of groceries			
37. Climbing nine steps (non-stop)			
38. Climbing 12 steps (non-stop)			
39. Walking ½ block uphill			
40. Walking ½ block uphill (non-stop)			
41. Shopping (by yourself)			
42. Washing clothes (by yourself)			
43. Walking one block on level ground			
44. Walking two blocks on level ground			
45. Walking one block on level ground (non-stop)			
46. Walking two blocks on level ground (non-stop)			
47. Scrubbing (floors, walls or cars)			
48. Making beds (changing sheets)			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
49. Sweeping			
50. Sweeping (five minutes non-stop)			
51. Carrying a large suitcase or bowling (one line)			
52. Vacuuming carpets			
53. Vacuuming carpets (five minutes non-stop)			
54. Painting (interior/exterior)			
55. Walking six blocks on level ground			
56. Walking six blocks on level ground (non-stop)			
57. Carrying out the garbage			
58. Carrying a heavy load of groceries			
59. Climbing 24 steps			
60. Climbing 36 steps			
61. Climbing 24 steps (non-stop)			
62. Climbing 36 steps (non-stop)			
63. Walking one mile			
64. Walking one mile (non-stop)			
65. Running 110 yards (100 meters) or playing softball/baseball			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
66. Dancing (social)			
67. Doing calisthenics or aerobic dancing (5 minutes non-stop)			
68. Mowing the lawn (power mower, but not a riding mower)			
69. Walking two miles			
70. Walking two miles (non-stop)			
71. Climbing 50 steps			
72. Shoveling, digging or spading			
73. Shoveling, digging or spading (five minutes non-stop)			
74. Climbing 50 steps (non-stop)			
75. Walking three miles or golfing 18 holes without a riding cart			
76. Walking three miles (non-stop)			
77. Swimming 25 yards			
78. Swimming 25 yards (non-stop)			
79. Bicycling one mile			
80. Bicycling two miles			
81. Bicycling one mile (non-stop)			
82. Bicycling two miles (non-stop)			
83. Running or jogging ¼ mile			
84. Running or jogging ½ mile			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
85. Playing tennis or racquetball			
86. Playing basketball (game play)			
87. Running or jogging ¼ mile (non-stop)			
88. Running or jogging ½ mile (non-stop)			
89. Running or jogging one mile			
90. Running or jogging two miles			
91. Running or jogging three miles			
92. Running or jogging one mile in 12 minutes or less			
93. Running or jogging two miles in 20 minutes or less			
94. Running or jogging three miles in 30 minutes or less			

13.17.5 Component 4: Eyes

Patient Name: _____ Patient MR#: _____

Date of Assessment: _____

Assessed: Yes No Age Restriction

Reason if "NO":

1. **CAS - Initial assessment**

PLEASE ASSESS if patient is 9 years old and older

Please Check off the boxes (grade the worst eye)
1+ = few separated spots
2+ = many separated spots
3+ = confluent spots

None = 0		Mild = 1		Moderate = 2		Severe = 3	
Schirmer's without Anesthesia > 10 mm		Schirmer's without Anesthesia 7 to 10 mm		Schirmer's without Anesthesia 3 to 6 mm		Schirmer's without Anesthesia < 3 mm	X
No punctate keratopath		Mild punctate keratopathy		Moderate punctate keratopathy		Severe punctate keratopathy	X

Grade 0 No conjunctival disease	X	**Grade 1** conjunctival hyperemia occuring on the bulbar or palpebral conjuctiva.		**Grade 2** palpebral conjunctival fibrovascular changes occuring along the superior border of the upper eyelid, or the lower border of the tarsal plate of the lower eyelid, with or without conjuctival epithelial sloughing, involving < 25 % of the total surface area OR **Grade 3** palpebral conjunctival fibrovascular changes occuring along the superior border of the upper eyelid, or the lower border of the tarsal plate of the lower eyelid, involving 25 to 75 % of		**Grade 3** > 75 % of the total surface area with or without a cicatricial entropion.	

Schirmer's without Anesthesia: Rt eye____ mm Lf eye____mm
Schirmer's with Anesthesia*: Rt eye____ mm Lf eye____mm

Overall Stage (max 3) :------

Total Score (max 9): ---------

2. .Not in CAS - Ocular Symptoms

	Dryness				**Redness**				**Irritation**			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Right Eye		X				X				X		
Left Eye		X				X				X		

3. **Not in CAS - Recommended therapy:**

Recommended Therapy				
None	Ocular lubrication	topical restasis or topical corticosteroids	Punctual occlusion	Other
	X	X	X	discussed ASED and scleral contact lenses

4. Composite Assessment Scale:

Test	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Schirmer's Tear Test (without Anesthesia)	> 10 mm	7-10 mm	3-6 mm	< 3 mm
Punctate Keratopathy	None	1+ = few separated spots	2+ = many separated spots	3+ = confluent spots
Conjunctival Inflammation and Scarring (see scheme below)	No conjunctival disease	Grade 1	Grade 2 or 3	Grade 4

Examined by: ---------- ----------

Date

_____ _____ _____

Signature Printed Name Date

13.18 APPENDIX R: CHRONIC GVHD COMPOSITE ASSESSMENT SCALE BARTHEL INDEX SCORE

Patient Name:_____ MR #:_____

Rater Name: _____ Date: _____

Activity	Score	Ratings
Feeding		0=unable 5=needs help cutting, spreading butter, etc., or requires modified diet 10= independent
Bathing		0=dependent 5=independent
Grooming		0=needs help with personal care 5=independent with face/hair/teeth/shaving (implements provided)
Dressing		0=dependent 5=needs help but can do about half unaided 10= independent (including buttons, zippers, laces, etc.)
Bowels		0=incontinent (or needs to be given enemas) 5=occasional accidents 10= continent
Bladder		0=incontinent, or catherized and unable to manage alone 5=occasional accidents 10= continent
Toilet Use		0=dependent 5=needs some help, but can do something alone 10= independent (on and off, dressing and wiping)
Transfers (Bed to chair and Back)		0=Unable, no sitting balance 5=major help (one or two people, physical), can sit 10=Minor help (verbal or physical) 15=independent

Mobility (on level surfaces)		0=Immobile < 50 yards) 5=wheelchair independent, including corners>50 yards 10=walks with help of one person (verbal or physical)>50 yards 15=independent (may use any aid; for example cane or walker)>50 yards
Stairs		0=unable 5=needs help (verbal, physical, carrying aid) 10= independent

Total Score: (0-100) _____

_____ _____ _____

Signature: **Printed Name:** **Date:**

13.19 APPENDIX S: CHRONIC GVHD COMPOSITE ASSESSMENT SCALE FRENCHAY ACTIVITIES INDEX

Patient Name:_____MR #:_____

Rater Name: _____ Date: _____

In the last 3 months, how often have you undertaken:

Task Number	Task Description: Domestic Chores	Score	*Ratings:* *0=Never* *1= Less than once a week* *2=1-2 times per week* *3=Most days*
1.	Preparing main meals		
2.	Washing up after meals		
	Subtotal Domestic Chores : (__/6)		

In the last 3 months, how often have you undertaken:

Task Number	Task Description: Leisure/work	Score	*Ratings:* *0=Never* *1= 1-2 times in 3 months* *2= 3-12 times in 6 months* *3=At least weekly*
3.	Washing clothes		
4.	Light Housework		
5.	Heavy Housework		
6.	Local Shopping		
7.	Social Occasions		
8.	Walking outside for >15 minutes		
9.	Actively pursuing a hobby		

10.	Driving a car/going on bus		
	Subtotal Leisure/Work: (____/24)		

In the last 6 months how often have you undertaken:

Task Number	Task Description: Outdoor	Score	Ratings:
11.	Travel outing/car ride		*0=Never* *1=1-2 times in 6 months* *2=3-12 times in 6 months* *3= at last weekly*
12.	Gardening		*0=Never* *1=Light* *2=Moderate* *3=Heavy/All necessary*
13.	Household Maintenance		*0=Never* *1=Light* *2=Moderate* *3=Heavy/All necessary*
14.	Reading Books		*0=None* *1=1 in 6 months* *2=Less than 1 in 2 weeks* *3= More than 1 every 2 weeks*
15.	Gainful Work		*0=None* *1=Up to 10 hours/week* *2=10-30 hours/week* *3=Over 30 hours/week*
	Subtotal Outdoor: (___/15)		

Total Score: _____/45

_____ _____ _____
Signature: **Printed Name:** **Date:**

Revised guidelines for using the Frenchay Activities Index

The aim is to record activities which require some initiative from the patient. It is important to concentrate upon the patient's actual frequency of activity over the recent past, not distant past performance nor potential performance. One activity can only score on one item.

Specific item information:

1. Needs to play a substantial part in the organization, preparation and cooking of main meal. Not just making snacks or reheating prepared food.
2. Must do all or share equally, e.g. washing or wiping and putting away. Not just rinsing an occasional item.
3. Organization of washing and drying clothes, whether in washing machine, or by hand or at laundromat. Sharing task equally, e.g. loading, unloading, hanging, folding.
4. Dusting, polishing, ironing, tidying small objects or bedclothes. Anything heavier is included in item 5.
5. All heavier housework including changing beds, cleaning floors, fires and windows, vacuuming, moving chairs, etc.
6. Playing a substantial role in organizing and buying groceries, whether small or large amounts. Must go to the shop and not just push a cart. Can include collection of pension or going to the Post Office.
7. Going out to clubs, church activities, cinema, theatre, drinking, to dinner with friends, etc. May be transported there, provided patient takes an active part once arrived. Includes social activities at home, initiated by the patient, e.g. visits from family or friends not where main purpose is to provide care.
8. Sustained walking for at least 15 minutes (allowed short stops for breath). About one mile. Can include walking to do shopping, provided walks far enough.
9. Must require some 'active' participation and thought, e.g. propagating or caring for houseplants, knitting, painting, games, sports (not just watching sport on television). Can be mental activities, e.g. reading specialist magazines, doing the stocks and shares or window shopping for pleasure.
10. Must drive a car (not just be a passenger), or get to a bus/coach and travel on it independently.
11. Coach or rail trips or car rides to some place for pleasure. Not for a routine 'social outing' (i.e. shopping, going to local friends). Must involve some organization and decision-making by the patient. Excludes trips organized passively by institutions unless patient exercises choice on whether to go. The common factor is travel for pleasure. Holidays within the six months are divided into days per month e.g. a 7-day holiday equals 1 or 2 days per month.
12. Gardening outside:
    a. Light = occasional weeding or sweeping paths
    b. Moderate = regular weeding, raking, pruning, etc.
    c. Heavy = all necessary work including heavy digging.
13. Household maintenance:
    a. Light = repairing small items, replacing lamp lightbulb or plug

b. Moderate = spring cleaning, hanging a picture, routine car maintenance
c. Heavy = painting/decorating, most necessary household/car maintenance.

14. Must be full-length books, not periodicals, magazines or newspapers. Can be talking books.

15. Work for which the patient is paid, not voluntary work. The time worked should be averaged out over six months. For example, one month working for 18 hours/week over the six-month period would be scored as 'up to 10 hours/week'.

13.20 APPENDIX T: QUALITY OF LIFE ASSESSMENTS (OBTAINED AT BASELINE THEN YEARLY)

FACT-BMT (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT 10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate (e.g., reading)	0	1	2	3	4
BMT 11	I have frequent colds/infections	0	1	2	3	4
BMT 12	My eyesight is blurry	0	1	2	3	4
BMT 13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT 14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT 15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT 16	I have trouble with my bowels	0	1	2	3	4
BMT 17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT 18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

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FACT-BMT (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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FACT-BMT (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT 10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate (e.g., reading)	0	1	2	3	4
BMT 11	I have frequent colds/infections	0	1	2	3	4
BMT 12	My eyesight is blurry	0	1	2	3	4
BMT 13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT 14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT 15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT 16	I have trouble with my bowels	0	1	2	3	4
BMT 17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT 18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

US English
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Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

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3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

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6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h Have you been happy?	☐1	☐2	☐3	☐4	☐5
i Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

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11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d My health is excellent	☐1	☐2	☐3	☐4	☐5

THANK YOU FOR COMPLETING THESE QUESTIONS!

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Today's Date: _____ MR#/Name: _____

B. CHRONIC GVHD ACTIVITY ASSESSMENT-PATIENT SELF REPORT

Symptoms **Please rate how severe the following symptoms have been in the last seven days. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.**	**Not Present** 0	1	2	3	4	5	6	7	8	9	**As Bad As You Can Imagine** 10
Your **skin itching** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth dryness** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth pain** at its WORST?	O	O	O	O	O	O	O	O	O	O	O
Your **mouth sensitivity** at its WORST?	O	O	O	O	O	O	O	O	O	O	O

Eyes	What is your main complaint with regard to your eyes?	
	Please rate how severe is this eye symptom, between 0 (not at all severe) and 10 (most severe):	0 1 2 3 4 5 6 7 8 9 10
Vulvovaginal Symptom (females only)	Do you have any burning, pain or discomfort in the area of your vagina, vulva or labia? **OR** Do you have any discomfort or pain with sexual intercourse?	○ Yes ○ No ○ Not applicable

Patient Global Ratings:

1. Overall, do you think that your chronic graft versus host disease is mild, moderate or severe?
1= mild
2=moderate
3=severe

2. Please circle the number indicating how severe your chronic graft versus host disease symptoms are, where 0 is cGvHD symptoms that are not at all severe and 10 is the most severe chronic GvHD symptoms possible.

0 1 2 3 4 5 6 7 8 9 10

cGvHD symptoms not at all severe — Most severe cGvHD symptoms possible

3. Compared to a month ago, overall would you say that your cGvHD symptoms are:

+3= Very much better
+2= Moderately better
+1=A little better
0= About the same
-1=A little worse
-2=Moderately worse
-3=Very much worse

Attach copies of:

Adults (persons 18 years or older):
-Lee cGvHD Symptom Scale
-Human Activity Profile
-SF036
-FACT-BMT

Children/Adolescents (persons 17 years or younger):
-Lee cGvHD Symptom Scale (persons 8-12 years old may complete with help of the health care professional)
-ASK-p38 Activities Scale for Kids
-VARNI-Generic and Disease Specific Inventory

Today's Date: _____ MR#/Name: _____

C. Human Activity Profile

Instructions

- Please check each activity according to these directions:
- Check Column 1 ("Still Doing This Activity") if:
- You completed the activity unassisted the last time you had the need or opportunity to do so.
- Check Column 2 ("Have Stopped Doing This Activity") if:
- You have engaged in the activity in the past, but you probably would not perform the activity today even if the opportunity should arise.
- Check Column 3 ("Never Did This Activity") if:
- You have never engaged in the specific activity.

Human Activity Profile Test	**Still doing this activity**	**Have stopped doing this activity**	**Never did this activity**
1. Getting in and out of chairs or bed (without assistance)			
2. Listening to the radio			
3. Reading books, magazines or newspapers			
4. Writing (letters, notes)			
5. Working at a desk or table			
6. Standing (for more than one minute)			
7. Standing (for more than five minutes)			
8. Dressing or undressing (without assistance)			
9. Getting clothes from drawers or closets			
10. Getting in or out of a car (without assistance)			
11. Dining at a restaurant			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
12. Playing cards/table games			
13. Taking a bath (no assistance needed)			
14. Putting on shoes, stockings or socks (no assistance needed)			
15. Attending a movie, play, church event or sports activity			
16. Walking 30 yards (27 meters)			
17. Walking 30 yards (non-stop)			
18. Dressing/undressing (no rest or break needed)			
19.Using public transportation or driving a car (100 miles or less)			
20. Using public transportation or driving a car (99 miles or more)			
21. Cooking your own meals			
22. Washing or drying dishes			
23. Putting groceries on shelves			
24. Ironing or folding clothes			
25. Dusting/polishing furniture or polishing cars			
26. Showering			
27. Climbing six steps			
28. Climbing six steps (non-stop)			
29. Climbing nine steps			
30. Climbing 12 steps			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
31. Walking ½ block on level ground			
32. Walking ½ block on level ground (non-stop)			
33. Making a bed (not changing sheets)			
34. Cleaning windows			
35. Kneeling, squatting to do light work			
36. Carrying a light load of groceries			
37. Climbing nine steps (non-stop)			
38. Climbing 12 steps (non-stop)			
39. Walking ½ block uphill			
40. Walking ½ block uphill (non-stop)			
41. Shopping (by yourself)			
42. Washing clothes (by yourself)			
43. Walking one block on level ground			
44. Walking two blocks on level ground			
45. Walking one block on level ground (non-stop)			
46. Walking two blocks on level ground (non-stop)			
47. Scrubbing (floors, walls or cars)			
48. Making beds (changing sheets)			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
49. Sweeping			
50. Sweeping (five minutes non-stop)			
51. Carrying a large suitcase or bowling (one line)			
52. Vacuuming carpets			
53. Vacuuming carpets (five minutes non-stop)			
54. Painting (interior/exterior)			
55. Walking six blocks on level ground			
56. Walking six blocks on level ground (non-stop)			
57. Carrying out the garbage			
58. Carrying a heavy load of groceries			
59. Climbing 24 steps			
60. Climbing 36 steps			
61. Climbing 24 steps (non-stop)			
62. Climbing 36 steps (non-stop)			
63. Walking one mile			
64. Walking one mile (non-stop)			
65. Running 110 yards (100 meters) or playing softball/baseball			

Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
66. Dancing (social)			
67. Doing calisthenics or aerobic dancing (5 minutes non-stop)			
68. Mowing the lawn (power mower, but not a riding mower)			
69. Walking two miles			
70. Walking two miles (non-stop)			
71. Climbing 50 steps			
72. Shoveling, digging or spading			
73. Shoveling, digging or spading (five minutes non-stop)			
74. Climbing 50 steps (non-stop)			
75. Walking three miles or golfing 18 holes without a riding cart			
76. Walking three miles (non-stop)			
77. Swimming 25 yards			
78. Swimming 25 yards (non-stop)			
79. Bicycling one mile			
80. Bicycling two miles			
81. Bicycling one mile (non-stop)			
82. Bicycling two miles (non-stop)			
83. Running or jogging ¼ mile			
84. Running or jogging ½ mile			

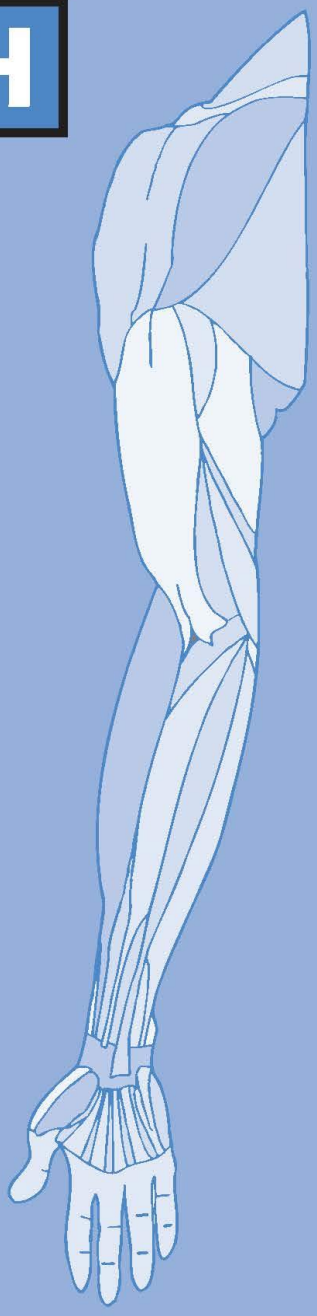
Human Activity Profile Test	Still doing this activity	Have stopped doing this activity	Never did this activity
85. Playing tennis or racquetball			
86. Playing basketball (game play)			
87. Running or jogging ¼ mile (non-stop)			
88. Running or jogging ½ mile (non-stop)			
89. Running or jogging one mile			
90. Running or jogging two miles			
91. Running or jogging three miles			
92. Running or jogging one mile in 12 minutes or less			
93. Running or jogging two miles in 20 minutes or less			
94. Running or jogging three miles in 30 minutes or less			

Today's Date: _____ MR#/Name: _____

D. Disabilities of the Arm, Shoulder and Hand.

DISABILITIES OF THE ARM, SHOULDER AND HAND

THE DASH



INSTRUCTIONS

This questionnaire asks about your symptoms as well as your ability to perform certain activities.

Please answer *every question*, based on your condition in the last week, by circling the appropriate number.

If you did not have the opportunity to perform an activity in the past week, please make your *best estimate* on which response would be the most accurate.

It doesn't matter which hand or arm you use to perform the activity; please answer based on your ability regardless of how you perform the task.

Disabilities of the Arm, Shoulder and Hand

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Write.	1	2	3	4	5
3. Turn a key.	1	2	3	4	5
4. Prepare a meal.	1	2	3	4	5
5. Push open a heavy door.	1	2	3	4	5
6. Place an object on a shelf above your head.	1	2	3	4	5
7. Do heavy household chores (e.g., wash walls, wash floors).	1	2	3	4	5
8. Garden or do yard work.	1	2	3	4	5
9. Make a bed.	1	2	3	4	5
10. Carry a shopping bag or briefcase.	1	2	3	4	5
11. Carry a heavy object (over 10 lbs).	1	2	3	4	5
12. Change a lightbulb overhead.	1	2	3	4	5
13. Wash or blow dry your hair.	1	2	3	4	5
14. Wash your back.	1	2	3	4	5
15. Put on a pullover sweater.	1	2	3	4	5
16. Use a knife to cut food.	1	2	3	4	5
17. Recreational activities which require little effort (e.g., cardplaying, knitting, etc.).	1	2	3	4	5
18. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
19. Recreational activities in which you move your arm freely (e.g., playing frisbee, badminton, etc.).	1	2	3	4	5
20. Manage transportation needs (getting from one place to another).	1	2	3	4	5
21. Sexual activities.	1	2	3	4	5

Disabilities of the Arm, Shoulder and Hand

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
22. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? *(circle number)*	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
23. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? *(circle number)*	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*

	NONE	MILD	MODERATE	SEVERE	EXTREME
24. Arm, shoulder or hand pain.	1	2	3	4	5
25. Arm, shoulder or hand pain when you performed any specific activity.	1	2	3	4	5
26. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5
27. Weakness in your arm, shoulder or hand.	1	2	3	4	5
28. Stiffness in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem. *(circle number)*	1	2	3	4	5

DASH DISABILITY/SYMPTOM SCORE = $\left[\left(\frac{\text{sum of n responses}}{n}\right) - 1\right] \times 25$, where n is equal to the number of completed responses.

A DASH score may <u>not</u> be calculated if there are greater than 3 missing items.

Today's Date: _____ MR#/Name: _____

E. PRO-CTCAE for Pomalidomide

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects.

For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days…

FATIGUE, TIREDNESS OR LACK OF ENERGY				
What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

NUMBNESS OR TINGLING IN YOUR HANDS OR FEET				
What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

PAIN				
How OFTEN did you have PAIN?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your PAIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PAIN INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

CONSTIPATION				
What was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

PROBLEMS WITH CONCENTRATION				
What was the SEVERITY of your PROBLEMS WITH CONCENTRATON at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much
TREMORS				
How OFTEN did you have TREMORS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your TREMORS at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
O Yes	O No
Please list any other symptoms:	
1.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
2.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
3.	What was the severity of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe

Today's Date: _____ MR#/Name: _____

INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0197 PRINCIPAL INVESTIGATOR: Steven Pavletic, MD

STUDY TITLE: A Randomized Phase 2 Single-Center Study of Pomalidomide for Chronic GvHD

Continuing Review Approved by the IRB on 12/19/16
Amendment Approved by the IRB on 05/17/17 (I) Date Posted to the Web: 05/26/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This study is being done to gain information on the use of an experimental medicine called pomalidomide (also called CC-4047) in people with chronic graft-versus-host disease (GvHD). We would like to obtain information on the efficacy of pomalidomide in people with chronic GvHD. Although pomalidomide has been already used in humans in cluding patients with chronic GvHD we will also look for any evidence of the side effects of treatment.

Pomalidomide is taken by mouth. It works by modifying the body's immune response. The effects of pomalidomide on the immune system may be beneficial in chronic GvHD. However, this has not been proven. Pomalidomide is chemically similar to the drug thalidomide, which

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has been shown to have beneficial effects in some people with chronic GvHD. However, thalidomide has not been approved by the Food and Drug Administration (FDA) for treatment of chronic GvHD.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have moderate or severe chronic GvHD that is not controlled by standard medicines such as corticosteroids or other treatments.

How many people will take part in this study?

We plan to enroll up to 35 subjects in this study.

Description of Research Study

In this study, we are studying the efficacy of different doses (high or low) of pomalidomide and their effect on chronic GvHD. The doses being studied are 0.5 mg and 2 mg per day. After you are accepted for this study and you choose to take part, you will be "randomized" into one of the two treatment groups (called "arms"). Randomization means that you are put into a group by chance. A computer program will place you in one of the treatment arms. Neither you nor your doctor can choose the treatment arm you will be in. All patients in the study will receive pomalidomide, just at different doses over time depending on their assigned treatment arm.

You will take pomalidomide capsules once a day in 4-week periods called cycles. All patients will start receiving the same dose of pomalidomide (0.5 mg). Patients in the 0.5 mg (low dose) treatment arm will stay at this same daily dose till the end of the study. Patients in the 2 mg treatment arm (high dose) will have their dose increased by 0.5 mg every two weeks until the 2 mg dose is reached. Pomalidomide has been given to humans at these doses before, but you will be still watched carefully for any side effects.

Pomalidomide therapy will continue for 6 cycles (6 months) unless your GvHD gets worse or you have unacceptable side effects from the pomalidomide. If your GvHD has improved at the end of the 6 cycles, you may be able to continue pomalidomide for up to 6 more cycles.

A detailed description of what will happen if you take part in this study, as well as a list of potential risks and discomforts associated with participation in the study are listed below.

What will happen if you take part in this research study?

Before you begin the study

You will need to have examinations, tests and procedures to see if you qualify for the study. Many of these tests are performed as part of your regular medical care or during the prior treatments for your GvHD. You will be asked to sign a separate consent describing the tests you will need to have done. In order for you to enroll in the Study you must follow the requirements of POMALYST REMS™ program.

After all of these examinations are performed we determine you are eligible for the trial, you will be asked to sign this informed consent agreeing to participate in this research study.

During the study

During the study, you will take pomalidomide capsules by mouth every day. Pomalidomide should be taken at about the same time each day. Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Patients are instructed to fast (water or clear fluids only) for at least 2 hours prior to taking a dose to at least 1 hour post-dosing. Pomalidomide should not be swallowed concurrently with other allowed medications while on-study.

You will be asked to complete a medication diary and to return any unused study drug and empty bottles to the clinic at each visit.

If you are taking other medications that increase the risk of blood clotting or you have other risk factors for blood clotting, you will take aspirin or another medicine to reduce the chance of blood clotting. All patients taking pomalidomide must follow strict guidelines for prevention of pregnancy. This is because there is a risk of harm to a fetus if pregnancy occurs while taking pomalidomide. These guidelines are outlined in the section on birth control below.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- Clinic visit, which will include a medical history, physical exam, and measurement of weight and vital signs every 2 weeks during the first 3 cycles, then at the beginning of every cycle, and when you stop taking pomalidomide
- Assessment of your GvHD, including questions about your symptoms, before you start pomalidomide, every 3 months while you are taking pomalidomide, and when you stop taking pomalidomide
- Blood draws for laboratory tests every 2 weeks during the first 3 cycles, then at the beginning of every cycle, and when you stop taking pomalidomide
- Urine tests before starting pomalidomide, every 3 months while you are taking pomalidomide, and when you stop taking pomalidomide
- Non-invasive imaging such as CT scans (a computerized x-ray examination) or MRI (an examination using magnetic field and radio waves) before starting pomalidomide and as medically necessary
- Lung function test every 3 months while you are taking pomalidomide, and when you stop taking pomalidomide
- EKG (a recording of the heart's electrical activity) and echocardiogram (an examination of your heart using sound waves) at the time of starting the study, monthy first three months, at six months and as medically necessary
- Pregnancy tests if you are a woman who is able to become pregnant, weekly during the first cycle, then every 28 days if you have regular periods or every 14 days if your

periods are irregular. We will provide a pregnancy test kit for you to use at home for the weeks you are not here at the NIH.

- As part of the evaluations for this study and of your graft-versus-host disease you will see specialists in dermatology (skin disease) and dentistry prior to study entry. You will see specialists in rehabilitation medicine, occupational therapy, ophthalmology (eyes) and gynecology (if female) up to two weeks after study entry. You will also see these specialists at 3-6 month intervals while you are on this study.

Tests and procedures that are either being tested in this study or being done to see how the drug is affecting your body:

- Blood draws to measure the levels of pomalidomide in your blood on the day you start pomalidomide, every 2 weeks for the first 3 months, then monthly until the 6-month visit. Each of these blood draws requires less than 2/3 teaspoons of blood (3 mL).
- Other blood samples will be collected for research at the same time points, about 50 mL (10 tea spoons of blood) except at the study beginning and after 3 and 6 months of therapy when a larger blood draw will be performed, about 20 teaspoons of blood (100 mL).
- You will be asked to give a sample of mouth saliva up to 10 cc (two teaspoons) before start of the therapy and at the end at six months or at permanently stopping pomalidomide therapy
- We would like your permission to collect biopsies (removal of a small bit of tissue for examination under a microscope) from your skin and mouth before starting pomalidomide and after 6 months or at permanently stopping the pomalidomide to study the effect of pomalidomide on immune response in these tissues.
- Photographs of your body cGVHD manifestations before starting the study and after 6 months or at permanently stopping pomalidomide

When you are finished taking the drugs (treatment)

When you are finished taking the drugs, we will continue to follow you for up to 2 years after you first started taking pomalidomide. The follow-up will include a clinic visit 3 months after your last dose of pomalidomide, and a phone call or visit to your regular doctor 1 and 2 years from the date you first started taking pomalidomide.

Study Chart

This chart outlines what will happen if you choose to participate:

Screening for Eligibility

- Medical history and physical exam
- Blood tests
- Chest CT scan
- Lung function test
- EKG and echocardiogram
- Pregnancy testing

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Treatment

Therapy:	Pomalidomide capsules by mouth once each day
Monitoring:	Review of side effects Medical history and physical exam Assessment of GvHD Blood and urine tests Non-invasive imaging Lung function testing EKG and echocardiogram Pregnancy testing and pregnancy prevention counseling
Research:	Blood, saliva, urine samples, Biopsies (optional)
Stop treatment:	Completion of 6 to 12 cycles of therapy Progressive GvHD Patient preference Unacceptable toxicity Other medical reasons

After Treatment

- Follow-up for up to 2 years after the first dose of

Birth Control

Pregnancy:

Pomalidomide was found to cause birth defects in an experimental study in animals. Pomalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Pomalidomide is therefore considered to have the potential to cause birth defects in humans. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females must not become pregnant while taking pomalidomide.

In order to participate in this study, you must register into and follow the requirements of the POMALYST REMS™ program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You will be required to receive counseling, follow the pregnancy testing and birth control requirements of the program that are appropriate for you and take surveys regarding your compliance with the POMALYST REMS™ program.

In addition, all patients taking pomalidomide must follow guidelines for prevention of pregnancy. This is because there is a risk of harm to a fetus if pregnancy occurs while taking pomalidomide. These guidelines are outlined below.
Note: By signing this consent you confirm that you understand and agree to receive counseling and to comply with the pregnancy precaution requirements of the POMALYST REMS™ program.

Screening:

- Pregnancy test, if applicable: If you are a female of childbearing potential, you will be required to have two negative pregnancy tests: the first test within 10-14 days before starting pomalidomide and the second test within 24 hours before your first dose of pomalidomide.
- For the purposes of this study, a female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

Pomalidomide is an analogue of thalidomide. Thalidomide is a known to cause severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. You have been informed that the risk of birth defects is unknown. If you are female, you agree not to become pregnant while taking pomalidomide.

Females:
If you are a female, you must not be pregnant.
You will be considered not of child bearing potential if you meet the following criteria:

- Absence of menstrual periods (natural menopause) for the past 24 consecutive months or
- Have had a hysterectomy (the surgical removal of the uterus) or both ovaries surgically removed

If you do not meet these criteria, you will be considered a female of child bearing potential. If there is ANY chance that you can become pregnant, you must follow the guidelines below.

If you **ARE** a female of childbearing potential, you will not be able to participate in this research study unless you have had two negative pregnancy tests, one within 10-14 days and one within 24 hours of starting pomalidomide.

In addition, with your doctor's knowledge and approval, you agree to use **TWO** reliable forms of birth control or practice complete abstinence from heterosexual intercourse during the following time periods related to this study:

- For at least 28 days before starting pomalidomide
- While taking pomalidomide
- During dose interruptions
- And for at least 28 days after you stop taking pomalidomide

You agree to inform the investigator immediately if:

- You have any reason to suspect you are pregnant
- You find that circumstances have changed and that there is a risk of becoming pregnant
- You have stopped using the approved forms of **TWO** reliable birth control methods
- You must talk to your doctor before changing any birth control methods

- The following methods of birth control are considered acceptable birth control methods:

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

Special Note: Certain HIV-protease inhibitors, griseofulvin, modafinil, pencillins, rifampin, rifabutin, phenytoin, carbamazepine, or certain herbal supplements such as St. John's Wort may reduce the effectiveness of hormonal contraceptives during and up to one month after discontinuation of these concomitant therapies.

Therefore, females of childbearing potential requiring treatment with one or more of these drugs must choose **ONE** non-hormonal method as the highly effective method of birth control (IUD, tubal ligation, partner's vasectomy) along with **ONE** of the additional effective methods (latex

condom, diaphragm, cervical cap) or abstain from heterosexual contact while taking pomalidomide.

You must use at least one highly effective method and one additional effective method of birth control **AT THE SAME TIME**. However, your doctor may recommend that you use two barrier methods for medical reasons.

If you have sex without using **TWO** reliable methods of birth control, or if for any reason you think you may be pregnant, you must **IMMEDIATELY** stop taking pomalidomide and tell your doctor.

You will have pregnancy tests before and during treatment, even if you agree not to have reproductive heterosexual intercourse. You will have a pregnancy test done by the doctor every week during the first 28 days of this study. You will then have a pregnancy test every 28 days during your participation in this study if your menstrual cycles are regular or every 14 days if your cycles are irregular. You will also have a pregnancy test if you miss your period or have unusual menstrual bleeding. In addition, you will have pregnancy tests when you stop taking pomalidomide and at day 28 after you stop taking pomalidomide if your menstrual cycles are regular. If your menstrual cycles are irregular, you will have pregnancy tests when you stop taking pomalidomide and at days 14 and 28 after you stop taking pomalidomide.

You must not breastfeed a baby while you are participating in this study and for at least 28 days after you stop taking pomalidomide.

You must **NEVER** share pomalidomide (or other study drugs) with someone else. You must **NEVER** donate blood while you are participating in this study and for at least 28 days after you stop taking pomalidomide. You will be counseled at least every 28 days and at discontinuation from the trial about not sharing pomalidomide (and other study drugs), the potential risks of fetal exposure, and abstaining from blood donations.

If you have any reason to suspect you are pregnant, you must **IMMEDIATELY** stop taking pomalidomide and tell your doctor. If you have a positive pregnancy test while participating in this study, you must **IMMEDIATELY** stop taking pomalidomide and tell your study doctor. If you have a positive pregnancy test within 28 days after you stop taking pomalidomide, you must **IMMEDIATELY** tell your doctor.

Study subjects who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30 days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).

Males:
You have been informed about the risk of birth defects and you agree to use a latex condom every time you have sex with a female of childbearing potential while you are participating in this study and for at least 28 days after you stop taking pomalidomide, even if you have had a successful vasectomy. You must tell your doctor if you have sex with a female of childbearing

potential without using a latex condom or if you think for any reason your partner may be pregnant.

You must **NEVER** share pomalidomide (or other study drugs) with someone else. You must **NEVER** donate blood, sperm, or semen while you are participating in this study and for at least 28 days after you stop taking pomalidomide. You will be counseled at least every 28 days regarding abstaining from donating blood, sperm, or semen; birth control requirements; not sharing pomalidomide (and other study drugs); and the potential risks of fetal exposure.

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

There is always a risk involved in taking any drugs, but you will be carefully monitored for any problems and you are encouraged to report anything that is bothering you. There may be risks or side effects of the study drug that are unknown or cannot be predicted at this time. You should not hesitate to report anything that upsets you or may be troubling you to your study physician or member of the study team, even if you do not think it is connected to taking the study drug.

If you have any questions you should contact the study physician or member of the study team. You will receive any new information during the course of the study concerning significant treatment findings from this study or others (good or bad) that may affect your willingness to continue. In addition to the risks of the study drug, pomalidomide, described below, you may experience discomfort associated with blood draws and tissue biopsies (whether clinically indicated or related to research) while participating in the study.

Risks of pomalidomide:

Pomalidomide has been studied in healthy volunteers and in patients with cancer of the blood and other organs of the body, as well as in patients with other diseases. As with any other experimental treatment, there may be side effects or risks associated with pomalidomide, some of which are not yet known. As of March 1, 2011, about 517 patients participating in Celgene-sponsored studies had taken pomalidomide, and the risks below are drawn from reports from these patients.

The side effects that patients had after starting pomalidomide in completed and ongoing studies are noted below. Your health care team may give you medicines to help lessen or treat side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long-lasting or may never go away, or can cause death. It is not yet possible to know for certain which of the reported side effects are directly due to pomalidomide itself. As pomalidomide is being studied as a treatment for serious diseases, some of the reported conditions could be from the disease itself, or other pre-existing diseases, or other drugs the patient may have been taking. It should not therefore be assumed that all the side effects listed below were caused by pomalidomide.

Pomalidomide can cause a decrease in the number of white blood cells, red blood cells, platelets, and/or neutrophils (a type of white blood cell). White blood cells are cells of your immune system. In some patients, a decrease in blood cells can be serious and may require you to stop treatment. A decrease in white blood cells and/or neutrophils may lead to fever and/or a life-threatening infection. The red blood cells carry oxygen to your organs. A decrease in red blood cells can lead to fatigue or feeling tired. A decrease in platelets may lead to bleeding and require stopping treatment. Other laboratory values may become abnormal, as well.

Side effects reported as serious at least once are **bolded.**

Likely (reported in more than 10% of patients)	**Less Likely** (reported in 5 to 10% of patients)	**Rare but Serious** (reported in less than 5% of patients)
• **Low white blood cell count** • Constipation • Nausea • Skin rashes • **Fatigue or tiredness** • **Shortness of breath** • **Lung infection** • Cough • Dizziness • Muscle aches or pains • Skin tingling	• **Fever** • **Low platelet count** • Inflammation of the throat • Skin itching • Swelling • **Diarrhea (loose stool)** • Muscle cramps • **Headache** • **Pain in chest, back, joints, arms or legs** • Dry skin and itch • Decreased sensitivity to touch	• **Fever and infection when the white blood cell count is low** • **Decrease in red blood cells, which carry oxygen** • **Severe infection of the bloodstream** • **Urinary tract infection** • **Dehydration (too little fluids in the body)** • **Too much calcium in the blood** • **Kidneys not working correctly** • **Cancer of the white blood cells, adrenal gland, bladder, kidney, or thyroid** • **Confusion** • **Blood clot in the veins or lung** • **Atrial fibrillation (when the top of your heart quivers instead of beating)**

Deep vein thrombosis and pulmonary embolism

Medications in the same family of medications as pomalidomide have shown an increased risk of deep vein thrombosis (blood clot in a larger blood vessel) and pulmonary embolism (a blood clot in or around the lungs) in some subjects with certain medical conditions. If you are at increased risk for blood clots due to certain medical conditions or other medications you may be taking, you will receive either aspirin or another medicine to reduce the chance of blood clotting while you are receiving pomalidomide.

Reproductive Risks

As indicated in the section on birth control, pomalidomide is related to thalidomide, a drug known to cause severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Additional precautions

Other than the patient, women who are able to become pregnant and men who are able to father a child should not touch or handle the pomalidomide capsules.

While in this study, if any physician or healthcare provider, other than your study physician, prescribes medication(s) for you for another condition or reason, or you are taking any over-the-counter medications, vitamins, herbal, holistic or homeopathic remedies, please tell the study doctor or a member of the research team immediately. Please also let your study doctor know all of your present and past diseases and allergies. This is important because a possible interaction with some medications, vitamins, and remedies may cause serious side effects, and/or may still be unknown.

Potential Benefits of Participation

Are there benefits to taking part in this study?

No benefit can be promised to you for your participation in this study. We do not know if you will receive personal medical benefit directly from taking part in this study, although the knowledge gained from this study may help others in the future who have chronic GvHD. This study may lead to an increase in understanding of pomalidomide as therapy for chronic GvHD, and possibly better treatments based on results from this study for patients in the future. Potential benefits to you could include improvement in your GvHD or lessening of your symptoms that are caused by your GvHD. However, it is possible that you will not receive any benefit from participating.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

- Getting treatment or care for GvHD without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by GvHD. It does not treat the GvHD directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease worsens or comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if you do not follow the treatment plan, including steps to prevent getting pregnant and protecting others from pomalidomide

If this occurs, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up until that point may still be provided to Celgene or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using pomalidomide, developed by Celgene. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of pomalidomide.

Will my medical information be kept private?

We will do our best to make sure that the personal information in you medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Regulatory agencies in the United States
- NCI Institutional Review Board
- Qualified representatives from Celgene, the pharmaceutical company who produces pomalidomide.
- In order to obtain pomalidomide free of charge from Celgene, your name, address, phone, date of birth and the fact that you are participating in this trial will be disclosed to Celgene and its agents or vendors that supply pomalidomide and administer the POMALYST REMS™ program. By signing this consent form you agree to this disclosure.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Biopsies

Optional punch skin and oral biopsies will be performed. Prior to the biopsy, you will receive local anesthesia through a small injection into the area of skin or mouth mucosa surrounding the biopsy site. Samples will be removed with a needle during the biopsy (size of the pencil eraser). You may require a stitch after the biopsy. Risks of the biopsy include local oozing of blood or discomfort. Infection is a rare complication of skin/oral biopsies. The biopsies to be performed are exclusively for research purposes and will not benefit you. They might help other people in the future. Even if you sign "yes" to have the biopsies you can change your mind at any time. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care. Your permission for this will be obtained at the time of the biopsy.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that it may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Steven Pavletic, M.D., Building 10, Room 3-3330, Telephone: 240-760-6174. You may also call the Clinical Center Patient Representative at (301) 496-2626. If you have any questions about the use of your specimens and data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

_____ _____
Signature of Adult Patient/ Legal Representative Date

_____
Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

_____ _____
Signature of Parent(s)/ Guardian Date

_____
Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

_____ _____ _____
Signature of Parent(s)/Guardian Date Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM DECEMBER 19, 2016 THROUGH DECEMBER 18, 2017.

_____ _____ _____ _____
Signature of Investigator Date Signature of Witness Date

_____ _____
Print Name Print Name