Amendment

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Protocol Title: Multi-institutional Prospective Phase II Study of Montelukast for the Treatment of Bronchiolitis Obliterans following Allogeneic or Autologous Stem Cell Transplantation in Children and Adults

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* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** 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.

IRB Meeting Date: Expedited

DEC Clearance Date: 12/29/2016

Protocol Version Date: 12/27/2016

Abbreviated Title: Phase II Montelukast for BO
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Title of Study: Multi-institutional Prospective Phase II Study of Montelukast for the Treatment of Bronchiolitis Obliterans following Allogeneic or Autologous Stem Cell Transplantation in Children and Adults

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B. Obtaining identifiable private information about living individuals

C. Obtaining the voluntary informed consent of individuals to be subjects

D. Makes decisions about subject eligibility

E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes

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Commercial Agents: Montelukast

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PRECIS

Background

- Bronchiolitis obliterans (BO) is an insidious disease with high mortality following allogeneic blood or marrow transplantation (BMT). There are no consistently effective treatments for BO following BMT and the pathogenesis is largely unknown.
- The mechanisms underlying similar immune-mediated lung destructive processes are better elucidated. Rejection following allogeneic lung transplantation and scleroderma lung disease result from analogous immunologically mediated destruction of lung tissue leading to similar pathologic and clinical presentations to post-BMT BO.
- Increased leukotriene production has recently been implicated in the development of both post-lung transplant BO and scleroderma lung disease in animal models and patient studies.
- Montelukast (singulair) is an approved, well-tolerated, oral agent that inhibits leukotriene action in lung inflammation. This agent has been extensively used in children and adults to treat asthma with an excellent safety profile.

Objectives

- To evaluate if montelukast stabilizes or improves pulmonary function in patients with BO after BMT using FEV-1 changes as primary endpoints.

Eligibility

- Patients $\geq$ 6 years old with bronchiolitis obliterans following stem cell transplantation for any disease indication may be enrolled.

Design

- This is a prospective phase II study, the primary aim of which is to assess whether montelukast improves or stabilizes the pulmonary function of patients with BO after BMT.
- Primary outcome data will be analyzed in 2 ways. 1) The proportion of patients with stable or improved percent predicted of FEV-1 will be compared against benchmark data obtained from a literature review. 2) The slope of FEV-1 before and after the introduction of montelukast will be compared.
- Pediatric and adult patients with BO following BMT will receive approved doses of montelukast continuously for 6 cycles of 30 days.
- The planned length of the study would be 2 years per patient with primary endpoint after 6 cycles of therapy, permitting sufficient time to determine safety and meet other endpoints.
- This phase II trial will be conducted at 2 institutions: NIH and Fred Hutchinson Cancer Research Center (FHCRC). Forty-five patients will be enrolled on this trial.

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1 INTRODUCTION

1.1 Study Objectives

1.1.1 Primary Study Objectives

To determine if montelukast results in stabilization or improvement in pulmonary function in patients with BO following stem cell transplant using the FEV-1 measurement after six cycles (of 30 continuous days) by comparing the absolute change in predicted FEV-1in montelukast-treated patients to a benchmark control from publications and by comparing the FEV-1 slope (of the absolute value) before and after montelukast exposure.

1.1.2 Secondary Study Objectives

1.1.2.1 To confirm the safety profile of montelukast

1.1.2.2 To determine if montelukast improves oxygen saturation or decreases oxygen requirement in pediatric and adult patients with bronchiolitis obliterans following stem cell transplant.

1.1.2.3 To assess if montelukast improves other pulmonary function parameters to include: FEF25-75, RV, DLC02, and ratio of FEV-1/FVC and FEV-1/SVC.

1.1.2.4 To determine if montelukast improves pulmonary endurance using the 2 and 6 minute walk test.

1.1.2.5 To evaluate if montelukast decreases leukotriene levels (LTB4 and CysLT) in the urine or blood or leukotriene receptor expression (BLT or CysLT) on activated circulating immune cells. To determine if improvement in pulmonary function correlates with decreased leukotriene levels or leukotriene receptor expression on activated immune cells.

1.1.2.6 To investigate whether patients experience improvements in other chronic graft-versus-host disease manifestations or quality of life and function parameters while receiving montelukast.

1.1.2.7 To evaluate if the introduction of montelukast impacts overall survival of patients with bronchiolitis obliterans after stem cell transplant at study conclusion (2 years).

1.2 Background and Rationale

1.2.1 Bronchiolitis Obliterans

Bronchiolitis obliterans (BO) is a progressive insidious disease with a high mortality following allogeneic stem cell or blood and marrow transplantation (BMT). [1, 2] Although BO is a rare complication of BMT, affecting approximately 2-10% of BMT recipients, it causes significant morbidity and mortality for affected patients. [2-4] Studies suggest that less than 20% of patients will improve with standard therapies and that 65% or more of patients with BO and chronic GVHD

will die within 3 years of the diagnosis of BO regardless of the therapies instituted.[1, 5, 6] In all of these trials, standard treatments included immunosuppression with various combinations of medications including: steroids, cyclosporine, azatioprine, and antithymocyte globulin. For patients not responding to the initial course of immunosuppression with these medications, 2 year survival was 20% and 5 year survival only 13% from the diagnosis of BO.[2] Although the pathogenesis of BO remains unknown, BO is thought to be a manifestation of chronic graft versus host disease following BMT and commonly occurs in the setting of other chronic GVHD manifestations. Clinically, this syndrome is defined by significant airway obstruction on pulmonary function tests with a diminished FEV-1 (forced expiratory volume in 1 second) in the absence of infectious etiology. Decreases in FEV-1 demonstrate disease progression; BO patients with improvements in FEV1 have increased survival following BO diagnosis.[2] Pathologically, the lung tissue demonstrates evidence of bronchiolar inflammation and obstruction of the lumen. Neutrophil or lymphocyte infiltration has also been observed in biopsy specimens. Anecdotal evidence has provided the basis for immunosuppressive therapy with steroids, extracorporeal photopheresis, and tumor necrosis factor blockade.[7-9] However, these agents have had little historic success in arresting the disease process in the majority of patients. Furthermore, these treatments have significant toxicities including the development of fatal infections, prompting a need for novel treatment strategies based on improved scientific understanding of disease mechanism.

Little is known regarding the genesis of bronchiolitis obliterans following bone marrow transplant due to the rarity of this disease and the lack of good animal models. However, two conceptually and clinically similar diseases have better defined animal models providing insights into their mechanism: lung transplant recipients who experience rejection of the allogeneic lung and scleroderma lung patients who have an autoimmune fibrosis of the lung parenchyma. Lung transplant recipients who develop rejection display strikingly similar findings to BMT BO as defined by: decreased pulmonary function tests with an obstructive defect, similar radiographic opacities, and biopsy specimens characterized by inflammation of the bronchioles and bronchiectasis.[10] In scleroderma lung disease (SLD), although many patients have a restrictive defect, a subset has demonstrated an obstructive pattern on pulmonary function tests. Pathologically, a parallel pattern to BMT BO with bronchiectasis and inflammatory cell infiltrate accompanying fibrosis are commonly evident.[11] In both SLD and lung transplant rejection, good rodent models have demonstrated that lymphocytic infiltration with activated CD4+ and CD8+ T cells is a critical early event.[12, 13]

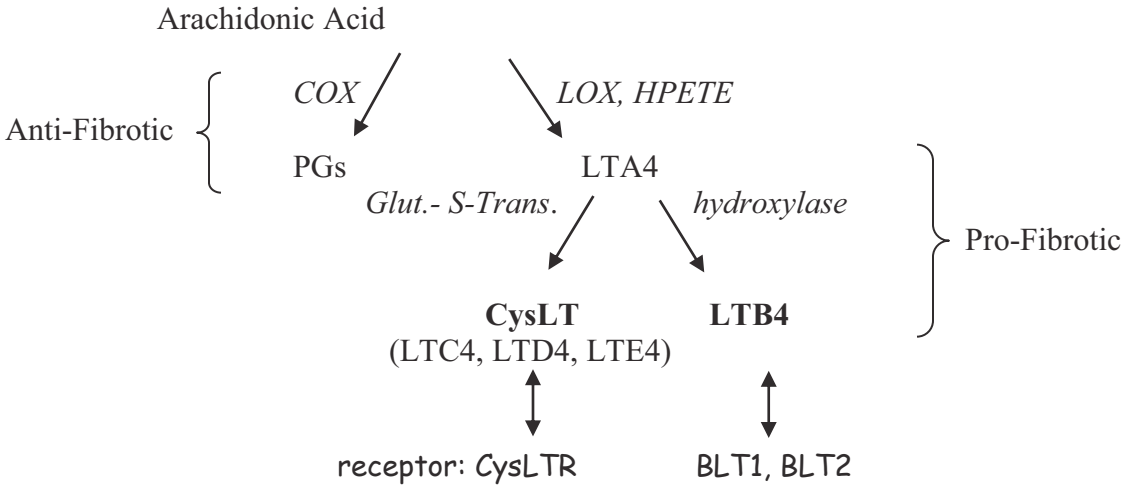
1.2.2 Leukotrienes are implicated in Auto- and Allo-immune mediated Lung Fibrosis

Leukotrienes are lipid inflammatory mediators that have been classically associated with the inflammatory lung disease asthma. Recent literature has implicated leukotriene production in the genesis of bronchiolitis obliterans following lung transplant and SLD. Increased levels of leukotrienes (LTB4 and LTE4) were demonstrated in the bronchoalveolar lavage fluid of patients with SLD as compared to either healthy controls or patients with scleroderma without lung pathology [14]. These elevated levels also correlated with diminished lung function in this cohort. Increased expression activation of 5-lipoxygenase, the enzyme responsible for leukotriene production, has been demonstrated in systemic sclerosis disease as well.[15] In lung transplant recipients, enhanced expression of leukotriene receptor BLT-1 on activated CD8+ T cells correlated with acute rejection of the lung in both mouse models and patients with lung rejection.[16] In this murine model, major mismatched tracheas were transplanted into wildtype mice. BLT-1 receptor

expression was 180 fold higher on CD8+ T cells and 1.4 fold higher on CD4+ T cells in the mice with mismatched tracheal transplants. BLT-1 was shown to be instrumental in tracheal rejection using BLT-1 knock out mice. Transfer of mismatched tracheas into BLT-1 knock out mice resulted in significantly less fibrosis and pathology than in wild type; these grafts appeared similar to syngeneic transplanted controls. This group also demonstrated similar improvements in pathology following an inhibitor of BLT-1 in another murine model of transplant rejection. These studies suggest that leukotriene production may be a key player in the genesis of antigen-driven immune system mediated bronchiolitis in murine and human models.

Leukotrienes are one of two main products derived from the breakdown of arachidonic acid; there is evidence that the balance of products from this pathway is critical to the nature of the aberrant inflammatory response in immune lung diseases (figure 1). Arachidonic acid is metabolized into: 1) prostaglandins (PGs) using cyclooxygenase (COX) and 2) leukotriene A4 (LTA4) via 5-lipoxygenase (LOX) and hydroperoxyeicosatetraenoic acids (HPETE). Leukotrienes are pro-fibrotic agents, activating fibroblasts and enhancing collagen deposition, while prostaglandins inhibit fibroblast proliferation and collagen synthesis. Thus, it has been hypothesized ed that pulmonary fibrosis results in part from an imbalance in the breakdown of arachidonic acid, favoring the production of leukotrienes while decreasing prostaglandin formation. Support for this theory includes a 5 to 15 fold increase in leukotriene levels in lung tissue homogenates from patients with idiopathic lung fibrosis.[17] Enhanced activation of LOX (important for LT synthesis) was demonstrated in this study as well. Two large groups of leukotrienes have been shown to promote and perpetuate different inflammatory responses: 1) LTB4 and 2) the cysteinyl leukotrienes (CysLT: LTC4, LTD4, LTE4). Both LTB4 and the CysLT are products of the brief intermediate of LTA4 using hydroxylase for LTB4 and Glutathione-S-transferase for CysLT. Hematopoeitic stem cells produce and respond to leukotrienes. Neutrophils and alveolar macrophages largely produce LTB4; eosinophils, dendritic cells, alveolar macrophages, and mast cells secrete primarily the CysLT. LTB4 has been shown to induce fibroblast migration. CysLT further promote lung fibrosis by inducing fibroblast propogation and collagen production. In addition, leukotrienes provide chemotaxis and survival signals for many immune system mediators. The receptors for LTB4, BLT1 and 2, have been increased on activated effector CD4+ and CD8+ T cells within bronchoalveolar lavage fluid.[18] The CysLT receptors, termed CysLTR 1 and 2, are present on alveolar macrophages, eosinophils, and mast cells. Murine studies have also demonstrated that CysLT provides a chemotactic signal for activated alpha beta and gamma delta T cells and that these activated T cells up-regulate the CysLTR.[19] Recent murine studies have also implicated the CysLTs in the genesis of CD4+ T cell-mediated inflammation and in augmenting the antigen-presenting capacity of murine dendritic cells. [20] Since both BLT-1 and CysLT have been shown to be upregulated on activated leukocytes, to be chemotactic signals for lymphocytes, and to induce pulmonary fibrosis, both leukotrienes are excellent candidates for a central role in post-BMT BO inflammation.

Figure 1: Arachidonic Acid Pathway:



Abbreviations: Lox- 5-Lypooxygenase; HPETE-Hydroperoxyeicosatetraenoic acids; Cox- Cycloxeganase; PGs- Prostaglandins; Glut.S.Trans.-Glutathione-S-transferase; LT- Leukotriene; CysLT- Cysteinyl leukotriene.

1.2.3 Translational Studies linking Leukotriene Synthesis and GVHD

While leukotriene synthesis has not been evaluated in BO following marrow transplant, there are two papers linking the systemic production of leukotrienes with graft-versus-host disease (GVHD). Takatsuka et al. correlated increased blood LTB4 levels with the severity of intestinal GVHD.[21] The second paper described a novel sensitive and specific urine proteomic pattern of GVHD.[22] One of the two identifiable proteins evident in the pattern was a product of the LTA4 hydrolase (which generates LTB4). In addition, eosinophilia has been correlated with the development of chronic GVHD as well as leukotriene-mediated lung damage.[23, 24] Collectively, the pathophysiology of LTs in inducing lung fibrosis, the data for increased leukotriene production in rejection after lung transplant and in SLD, and the LT data in GVHD, suggest that leukotriene production may be important in the genesis of BO after marrow transplant.

1.2.4 Montelukast Mechanism of Action

Montelukast is a U.S. Food and Drug Administration (FDA) approved oral agent that inhibits the action of cysteinyl leukotrienes. Montelukast is an antagonist to the cysteinyl leukotriene receptor and thus blocks the action of Cysteinyl leukotrienes (LTC4, LTD4, LTE4). There is evidence that montelukast decreases T cell proliferation and increases IFN gamma secretion as well.[25]

1.2.5 Montelukast Safety Profile

Montelukast has been given to over 2 million patients of which 220,000 have been pediatric patients.[26] Minimal toxicities have been reported in a prospective study of 2600 adult and adolescent patients, including fever, pain, cough, and liver function elevations in less than 4% of patients. More importantly, the incidence of all toxicities, including headache in 18% of patients, was the same in the placebo and montelukast-treated groups. (See section 8.1.10.)

1.2.6 Montelukast Pharmacology

Montelukast is orally absorbed with a bioavailability of 73% in a fasting individual.[26] The effect of fasting has not been shown to be clinically relevant. The drug is greater than 99% protein bound with no discernable animal data to indicate it crosses the blood brain barrier.[26] It is metabolized in the liver by the P450 CYP 3A4 and 2C9 enzymes. However, extensive testing has failed to demonstrate drug interactions due to this metabolism for fexofenadine, prednisolong, warfarin, and theophylline.[26] However, CYP 3A4 inducers such as rifampin and Phenobarbital did result a 40% decrease in the area of the curve of montelukast. [26]

Although montelukast is nearly entirely metabolized in the liver and excreted in bile, even patients with moderate hepatic insufficiency have been able to appropriately metabolize montelukast. There is no data for patients with severe liver toxicity. Patients with phenylketonuria should not take montelukast in the chewable form (which contains phenylalanine).

1.2.7 Clinical Data for the Administration of Montelukast for the Therapy of Bronchiolitis Obliterans after BMT

Montelukast has been given to 4 patients for the therapy of the obstructive lung component of BO after BMT within our centers and has been well-tolerated by all 4. Patient 1 was a 6 year old girl, 4 years post-allogeneic bone marrow transplant, with a new diagnosis of BO by biopsy for increasing reticular infiltrates over 6 months noted on chest CT. The pulmonary function tests demonstrated 50% lung function (for weight and height). After several months of montelukast therapy without alteration of other therapies, the patient's pulmonary function was 100% of expected for weight and height. She has continued on montelukast for nearly 2 years with persistent PFTs of 100%. Patient 2 was a teen aged girl, several years post-allogeneic BMT, who developed progressive BO with pulmonary function tests at 8 % of normal with recurrent pneumothoraces. After 1 year of montelukast, her pulmonary function remains stable and there has been no further evidence of pneumothoraces. Patient 3 was an 11 year old girl, 2 years post-allo BMT, with 1 year history of severe BO with oxygen requirment, PFTs of 8% of normal, and multiple, recurrent, debilitating pneumothoraces. After 2 months on montelukast, the patient has not had follow-up PFTs, however, she remained free of subsequent pneumothoraces and was able to discontinue oxygen support. Finally, patient 4 was a 21 year old, 1.5 years post allo-BMT, with evidence of BO on lung biopsy. Although she has not had subsequent studies to evaluate for BO, she has tolerated montelukast without difficulty.

Additionally, a recent study was published evaluating montelukast therapy for a diverse array of GVHD complications.[27] This study demonstrated that montelukast was safe in this patient population. Although only 5 patients were enrolled with BO, 3 patients had evidence of improvement by FEV1 parameter. Furthermore, none of the patients with other manifestations of cGVHD developed BO during montelukast treatment.[27] This study also showed an improvement in other manifestations of chronic GVHD, including skin, liver, and gastrointestinal complications. Despite this fact, this protocol is not powered to study these manifestations. Patients with chronic GVHD of liver, skin, or gastrointestinal system are a heterogeneous group of patients with diverse

clinical and pathologic findings, even within a single diagnosis precluding rendering the study much larger and more complex. Furthermore, other treatment modalities have demonstrated efficacy in these cGVHD manifestations prompting ethical considerations regarding the restriction of known therapies for a phase II trial. Thus, this study focuses on a fairly homogeneous population with a homogenous pathologic and clinical disease presentation, for which no good therapy has been demonstrated.

Taken together, of the 9 patients who have received montelukast for the treatment of BO, 4 have had objective improvement by PFT evaluation, 2 have had progressive disease, and 3 have had stable disease. These cohorts suggest that a prospective trial to specifically evaluate the therapeutic potential of montelukast for BO after BMT is warranted.

1.2.8 Trial Plan

Recently, the NIH consortium has provided guidelines for the diagnosis and monitoring of chronic GVHD[28-30]. This study addresses bronchiolitis obliterans due to the lack of alternative therapies with proven efficacy for this disease and the high mortality associated with disease progression. Given the excellent toxicity profile of montelukast and the anecdotal suggestion of benefit for patients with early BO, the trial design is a prospective phase II study that will use two primary endpoints to evaluate drug efficacy: 1) the proportion of patients who maintain a stable or improving FEV-1 (as a percentage of predicted) and 2) the slope of FEV-1 change over time for each patient after montelukast exposure. For the first primary endpoint, the proportion of patients maintaining a stable or improving FEV-1 (percent of predicted) will be benchmarked against a population derived from the largest studies in BO published to date. Although published over a 15 year time frame, these studies all included the outcomes of patients treated with similar immunosuppressive regimens including: steroids +/- cyclosporine, +/- azathioprine, +/- antithymocyte globulin +/- thalidomide.[2, 10, 31, 32] None of these regimens was deemed to be superior in these retrospective analyses. Furthermore, although the exact inclusion criterion differs between historical studies and in this protocol, the majority of patients would fit criteria for all. Thus, the use of these publications for historical benchmark data is warranted. Taken together, with a conservative estimate of FEV-1 % change within a 6 month timeframe and using the definition of response in this protocol, 59% (66/111) of historical controls would be expected to have stable or responsive disease with standard therapies.[2, 10, 31, 32] This study will thus compare the FEV-1 response to 60% stable or improved in a six month time frame. To meet both primary endpoints, 45 patients will be accrued. Additional exploratory analyses will evaluate FEV-1 data at 1 and 2 years. The second primary endpoint will utilize each patient as his/her own control. A slope derived from the absolute values of FEV-1 will be compared before montelukast initiation and after montelukast exposure. For this measure, the response will be an increasing slope after montelukast initiation. Additionally, response rates of other pulmonary parameters will be evaluated to determine if montelukast provides a respiratory benefit that may be captured through other tests. These will include: oxygen saturation and requirement, pulmonary function parameters: FEV-1/FVC ratio and FEV-1/SVC ratio, RV, DLCO2 (adults only), and FEF25-75, 2 and 6 minute walk time, and quality of life measures. As the DLCO2 from PFTs may not be accurately captured in children, this value will be evaluated only for adults in this trial. Two year overall survival in montelukast-treated patients will also be compared to historical controls. Overall two-year survival data can be obtained from the two largest publications on BO; in both studies, overall survival is approximately 40% despite the 14-year difference in publication dates (further demonstrating the lack of progress made in the treatment of BO). [2, 31] In addition, leukotriene levels will be captured at various time points from

bronchoalveolar lavage fluid (single time point), blood, and urine with leukotriene receptor levels on circulating immune cells to determine if leukotriene production correlates with response to montelukast in BO after BMT. Finally, this study will collect data on other forms of chronic GVHD to evaluate if montelukast improves these manifestations in an exploratory analysis. Patients will be recruited nationwide to the two centers of participation in this trial. All data will be coordinated through NIH.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

2.1.1.1 Age ≥ 6 years old.

2.1.1.2 Diagnosis of bronchiolitis obliterans after allogeneic or autologous stem cell transplant. The criteria will be based on the definitions created by the NIH consortium on cGVHD.[29] As part of these criterion, for patients without pathologic evidence of BO, one other sign of chronic GVHD must be present. For diagnosis of cGVHD, a minimum of the following must be present: 1) a process distinct from that diagnosed as acute GVHD, 2) the presence of a diagnostic sign or a distinctive sign supported by another clinical or laboratory test, and 3) the exclusion of other pathologies (i.e. recurrent cancer, drug reaction or infection (see Appendix 5a for a list of diagnostic signs.) [28] To meet criteria for a diagnosis of bronchiolitis obliterans, patients must fulfill all 3 criteria. Prior lung tissue biopsy will be analyzed and confirmed to show evidence of bronchiolitis obliterans by the NCI Laboratory of Pathology if available. If tissue is not available for confirmation, a new biopsy will not be performed.

For bronchiolitis obliterans:

1. FEV1 ≤ 75% of predicted by pulmonary function evaluation for height & weight.
2. Evidence of air-trapping or small airway thickening or bronchiectasis on high resolution chest CT and RV or RV/FVC>120% and evidence of chronic GVHD of another organ, **OR** FEV1/ vital capacity (slow or forced VC whichever is larger) ratio < 5% of predicted for age or < 0.7, **OR** pathologic evidence of bronchiolar inflammation and obstruction of the lumen consistent with a diagnosis of BO. Pulmonary function tests will utilize body plethysmography not helium studies for pertinent values when there is a discrepancy if available.
3. Absence of active infection with appropriate investigation of any clinical symptoms to include radiographic, microbiologic, and pathologic studies as determined by the PI or LAI.

Patients must also have 2 PFT measurements with documented FEV1 values greater than 3 months apart to calculate the entry FEV1 slope. All available prior PFTs will be utilized for baseline slope calculation. For adult patients, the absolute FEV1 will be utilized for slope calculation; for pediatric patients, the percent predicted will be used. For patients enrolled after an acute decline following BMT without 2 post-BMT values greater than 3 months apart, the pre-BMT value may be utilized as the first value and the entry PFT value

may be the second for the slope calculation. The baseline and 6th-cycle PFT should be done at the accruing site.

2.1.1.3 Prior therapy: For patients with a chronic diagnosis of BO who have been on treatments, any prior therapy that has been administered chronically for > 3 months will be acceptable for enrollment as long as the patient has not demonstrated consistent improvement attributed to these agent in a one month (or more) period of observation preceding enrollment. For patients on steroids, **a steroid burst** exceeding an increase of ½ mg/kg/day will be considered for the start of the 3 month monitoring period. Notably, documented intercurrent infections that are treated with antimicrobials that result in improvements to, but not above previous baselines will not be considered an improvement attributable to immunosuppressive therapy. Patients who have had consistent improvements in the months preceding trial entry will not be eligible since there will be no way to discern improvement due to montelukast versus another therapy. Alternatively, a patient with a new diagnosis of bronchiolitis obliterans characterized by a new decrease in FEV1 is also eligible for this study. Notably, patients who have received bronchodilators or other pulmonary therapies may be included in this study as long as montelukast is not part of this regimen.

2.1.1.4 Performance status: Karnofsky or Lansky performance status $\geq$ 40%. (Appendix 1)

2.1.1.5 Ability to give informed consent. For patients < 18 years of age, their legal guardian must give informed consent. Pediatric patients will be included in an age appropriate discussion in accordance with NIH or participating institutional guidelines.

2.1.1.6 Hepatic function: Patients must have evidence of adequate liver function prior to enrollment defined by total bilirubin < 3 x the upper limit of normal and transaminases < 5 x the upper limit of normal for age appropriate indices.

2.1.1.7 Cardiac function: Patients must have evidence of adequate cardiac function prior to enrollment defined by ejection fraction greater than 25% performed within the last 6 months at NIH and absence of symptoms of cardiac disease at FHCRC.

2.1.1.8 Pulmonary function: Patients must have an FEV1 greater than or equal to 20% predicted for inclusion in this study.

2.1.2 Exclusion Criteria

2.1.2.1 Underlying disease status: Patients with tumor burden greater than minimal residual disease (i.e. tumor burden that can only be detected by molecular methods) would be excluded from this study.

2.1.2.2 Prior post-transplant treatment with montelukast or zakirlukast within the past 2 months and total duration of therapy does not exceed 12 months without documentation of failure by pulmonary function testing.

2.1.2.3 Clinically significant systemic illness with manifestations of significant organ dysfunction which in the judgment of Principal or Associate Investigator would render the patient unlikely to tolerate the protocol therapy or complete the study.

2.1.2.4 Patients must have been on their current cGVHD therapeutic regimen for at least 3 months with stable or decreasing FEV1 to be eligible for this trial. Any patient who has been on a therapy for less than 3 months for cGVHD will need to be monitored for 3 months without improvement in FEV1 prior to enrollment.

2.1.2.5 Ventilated patients are excluded.

2.1.2.6 Patients taking rifampin or phenobarbital as these medications alter the metabolism of montelukast.

2.1.2.7 Patients taking greater than one age-appropriate dose of ibuprofen or aspirin containing products per day that inhibit cyclooxygenase will be excluded from this trial. The acceptable upper limit for adult daily doses of aspirin is 650mg/day and 800mg/day of ibuprophen. For children, the acceptable upper limit of ibuprophen is one pediatric dose per day (less than 10 mg per kg to a maximum of 800 mg). Children should not take aspirin due to risk of Reye's syndrome unless specifically prescribed by their physician.

2.1.2.8 Patients with a history of allergy to montelukast.

2.1.2.9 Pregnant females and nursing mothers will be excluded from this trial due to unknown risks to the developing fetus. While on study, patients of child-bearing potential must be able to consent to utilize effective birth control measures.

2.2 Research Eligibility Evaluation (See Appendix 2)

2.2.1 Eligibility evaluation should include a thorough history and physical examination. The complete history should include documentation of medication list and allergies to exclude patients currently taking rifampin or phenobarbital and those who have demonstrated an allergy to montelukast. In addition, the last changes in medications and doses for BO or chronic GVHD must also be included in the detailed history to determine eligibility. Performance status and evidence for remission of malignant disease must also be documented.

2.2.2 Laboratory studies must include: complete blood counts with differential, complete chemistry panel with liver enzymes and bilirubin, and urine pregnancy test for females.

2.2.3 An echocardiogram should demonstrate adequate cardiac function and must have been performed within the last 6 months at NIH. At FHCRC, patients may undergo clinical assessment to determine adequate cardiac function. Echocardiogram is required for patients with clinical signs of cardiac dysfunction prior to enrollment.

2.2.4 Pulmonary function tests (PFTs) must be performed for eligibility and baseline FEV1/FVC and FEV1/SVC ratio, FEF 25-75, RV, RV/FVC, DLC02 (adults only) and pre and post-bronchodilator recorded. The post-bronchodilator FEV1 must be less than or equal to 75% of normal for height and age (pediatrics) or age (adult only) to be eligible. If the patient has been started on any new medication for chronic GVHD in the past 12 months, evidence of persistent severe BO (< 15% absolute change in predicted FEV-1) or worsening disease (> 15% absolute decrease in predicted FEV-1) must be documented on 2 FEV1 evaluations greater than 3 months apart.

2.2.5 Patients must have had an evaluation for possible infectious causes of diminished pulmonary function to be eligible for this trial. This may include, but is not limited to, a bronchoalveolar lavage and/or lung biopsy with pathogen stains and cultures, or aggressive blood work-up for evidence of infectious diseases. This must include a high resolution chest CT evaluate to identify possible infectious consolidations or infiltrates.

2.2.6 In the unlikely event that a patient is self-referred for this study, the patient's primary physician or principal investigator (if part of an ongoing research study) will be contacted prior to enrollment.

2.3 Registration Procedure:

2.3.1 Protocol "Entry date" is the day that consent forms have been signed by patient or parent guardian. "Treatment start date" is the day recipient begins montelukast therapy.

2.3.2 For subject registration at NCI: Authorized staff must register an eligible patient with NCI Central Registration Office (CRO) within 24 hours of signing consent. The patient must be registered prior to beginning this study. A registration Eligibility Checklist is available from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) for NCI patients and must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>. There is no reason to emergently begin this therapy as this is a phase II study for a chronic disease and this therapy would be unlikely to benefit a patient in the setting of an acute clinical deterioration. Once a patient is enrolled, the Central Registration office (CRO) will be notified by the enrolling institution's protocol

research nurse. After confirmation of eligibility at CRO, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of montelukast. Appendix 2 outlines a checklist for eligibility studies and follow-up procedures. Since this is a prospective phase II study, there is no randomization or multiple study arms. Verification of Registration will be forwarded electronically via e-mail to the research team.

2.3.3 For subject registration at non-NCI institutions:

Regardless of which institution the subject enroll at, all participating subjects will be registered at the NIH Clinical Center in order to receive an NIH ID number. (for sample handling and tracking). This does not requires the subject's presence at NIH.
Registration will be a two part process as patients are screened on this protocol. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator. Subjects that do not meet screening criteria should be removed from the study following the procedure in section **3.6.4**

3 STUDY IMPLEMENTATION

3.1 Study Design

This is a prospective phase II study of montelukast for the treatment of BO following allogeneic or autologous stem cell transplant. The purpose of this study is to determine if the administration of montelukast results in stabilization or improvement of pulmonary function in patients with BO after BMT. This study will also evaluate if there is a decrease in blood or urine leukotriene levels or in leukotriene receptor expression in activated immune cells in patients taking montelukast for BO after BMT.

FDA-approved doses of montelukast will be utilized. There is no dose escalation in this study.

Primary outcome data will be analyzed in 2 ways. First, the proportion of patients with stable or improved percent predicted of FEV-1 will be compared relative to a benchmark based on data obtained from the published literature. Second, each patient will also serve as his/her own control to compare a slope of FEV-1 change pre-study to the slope of FEV-1 change after montelukast exposure.

3.2 Drug Administration

Montelukast will be supplied in the age appropriate oral dosage tablet as indicated in the following table. Should dose modifications be necessary, these are listed as well. Doses will be given orally nightly as a tablet (for doses greater than 4 mg) and as ½ an oral tablet for the 2.5 mg dose. Treatment with montelukast will continue for 6 cycles of 30 days (180 total days) or until the primary end point is achieved continuously with physical examination and laboratory monitoring monthly (see Appendix 2).

	Montelukast	
Patient Age	Initial Dose	50% Dose Reduction
6-14 years	5 mg	2.5 mg
>14 years	10 mg	5 mg

3.3 Treatment Modifications

Grade 2-3 CTCAE events attributable to underlying disease or pre-existing prior to montelukast administration will not be reported as an adverse event. These pre-existing clinical events must be documented in the initial history and physical examination. Expected manifestations in this patient population would include those attributed to chronic GVHD or its therapy, including: fatigue, colitis, cushingoid appearance, anorexia, xerostomia, taste alteration, arthritis, weakness, fibrosis, sclerodermatous changes, hypo- or hyperpigmentation, myositis, osteoporosis or osteonecrosis, dry eyes, pain, dyspnea, vaginal irritation, nail changes, photosensitivity, pruritis, rash, ulcers, dentition abnormalities, growth failure, endocrine abnormalities, and liver enlargement with abnormal liver tests.

Treatment medications: Patients who develop grade 2 toxicity for greater than 7 days that is probably or definitely attributed to study drug should hold montelukast until the toxicity resolves ($\leq$ grade 1) and then restart at the same dose level. If grade 2 toxicity recurs that is probably or definitely attributable to study drug, the patient should be reduced to 50% of the dose for the remainder of the study (see section 3.2). Should toxicity recur after dose reduction, the patient should be taken off treatment (see Section 3.6). Patients will be taken off treatment and not restarted if they experience grade 4 toxicity attributable to montelukast.

Patients who develop grade 3 toxicity probably or definitely attributed to montelukast should stop the therapy. If the toxicity resolves ($\leq$ grade 2) within 14 days, patients may restart at 50% dose reduction. If toxicity recurs, the patient should be taken off treatment (see Section 3.6).
All patients who experience grade 4 toxicity will be taken off treatment and not restarted (see Section 3.6).

If the patient is unable to tolerate montelukast due to recurrent or severe toxicity, the PI or LAI will be notified of the AE and the patient will be placed off- treatment and only the data up to the off-treatment point will be analyzed.

3.4 On Study Protocol Evaluation: Appendix 2 A/B

3.4.1 Pre-treatment Evaluation: Pre-treatment evaluation must be conducted within 2 weeks of enrollment at one of the 2 cooperating institutions: National Institutes of Health or Fred Hutchinson Cancer Research Center with the exception of the quality of life (which must be done within 7 days) and bronchoalveolar lavage tests (which must be done within the preceding 3 months). Initial pre-treatment evaluation may be obtained during enrollment onto NIH Protocol #04-C-0281 entitled: "Prospective Assessment of Clinical and Biological Factors Determining Outcomes in Patients with Chronic Graft-Versus-Host Disease."

- History and Physical Examination: All patients should have a complete history (including pre-transplant history, transplant course, and post-transplant course) and physical examination including extensive documentation and scoring of any physical manifestations of possible chronic graft versus host disease. A 2 and 6 minute walking test of pulmonary endurance must be conducted and recorded per institutional guidelines. A history of patient or donor asthma must be recorded for subsequent analysis purposes. A positive history in either the patient or donor is not part of exclusion or inclusion criteria. All physical exam findings must be recorded and documented as described in Appendix 3-8.

- Laboratory studies must include the following:
  - Complete blood counts with differential.
  - Complete chemistry panel: sodium, potassium, chloride, CO2, blood urea nitrogen, creatinine, calcium, phosphorus, and magnesium.
  - Liver panel: ALT, AST, total and direct bilirubin.
  - Infectious disease screening: CMV PCR, HCV PCR (NIH only), blood culture, urine culture. This will be sent to Dr. Hakim's laboratory Building 10, Room 12C216, 10 Center Drive, Bethesda MD 20892 (301 402-3627). For NIH patients, HIV antibody testing will occur. The remaining infectious disease labs (CMV, blood cultures, and urine culture) will be processed at FHCRC.
  - Immunologic screening: Immunoglobulin levels (IgG, IgM, IgA, IgE), CD4/CD8 total numbers and ratio. For patients enrolled at the FHCRC, these tests will be sent to NIH for processing. Dr. Hakim's laboratory Building 10, Room 12C216, 10 Center Drive, Bethesda MD 20892 (301 402-3627).
  - Anti-topoisomerase antibody titer (baseline only) associated with autoimmune lung fibrosis.[33] For patients enrolled at the FHCRC, these tests will be sent to NIH for processing. Dr. Hakim's laboratory Building 10, Room 12C216, 10 Center Drive, Bethesda MD 20892 (301 402-3627).

- Pulmonary Function Tests (PFTs) for all patients greater than 6 years of age. Baseline FEV1, FEV1/SVC ratio, RV, RV/TLC, FEF25-75, and DLC02 must be recorded. Also, patients should have a pre and post bronchodilator evaluation. Pulmonary function will be expressed as a % of predicted for age for adults and by size for children. (The pulmonary function for children must be calculated using NHANES criteria when

available). Baseline and 6 cycle PFTs must be done at accruing site. Should there be a bronchodilator response, the post-bronchodilator FEV-1 will be considered the baseline value. Baseline, 3 month and 6 month on study, and 6 and 18 months post study drug PFT's (DLCO) will be adjusted for hemoglobin. Baseline PFT's will be repeated if the patient presents with signs and symptoms of an active infection after obtaining PFTs. The NHANES III method will be used for endpoint analysis.

- Radiographic Evaluation: All patients must have a routine chest CT and a CT in expiration (supine position). Any abnormalities concerning for infection on this CT necessitate a thorough work up for infectious etiology prior to study enrollment. This could include (but is not limited to): galactomannan level, CMV PCR, Mycoplasma PCR, legionella PCR, mycobacteria blood culture, bacterial blood culture, nasopharyngeal viral antigen panel and culture, bronchoalveolar lavage with stains and cultures for viral, bacterial, and fungal diseases. The radiographic technique for this scan at NIH for adult patients will use a newer technique for baseline and follow-up of patients after Amendment H. The new technique will capture evidence of air trapping with approximately 4 fold less radiation exposure than traditional high resolution CT in expiration (HRCT exposure to breasts 3.41 rem vs. new is 0.78 rem, HRCT 4.9 vs. new esophagus 1.02, lungs HRCT 4.34 vs. new 0.89, and thymus HRCT 4.9 rem vs. new 1.02 rem). The protocol is already established in the NIH radiology department for other protocols (e.g. NCT 00414648).

- Tissue Review: Tissue obtained from prior lung biopsy with evidence of BO will be reviewed to confirm the pathologic findings. Patients do not need to undergo a lung biopsy at the time of enrollment. As an optional adjunct to the study, should there be paraffin embedded tissue remaining from the diagnostic biopsy, extra slides will be requested for immunohistochemistry analysis of leukotriene production and cellular infiltrates.

- Cardiac Evaluation: All patients will undergo ECG prior to entry to evaluate organ function at NIH. If this has been performed in the last 6 months, documentation of adequate function is sufficient for enrollment. This test is not required at FHCRC or other non-NCI sites.

- Leukotriene production studies: Blood and urine will be collected to measure leukotriene levels (Cysteinyl and LTB4). Blood will also be processed for multiparameter flow cytometry to measure leukotriene receptor levels on circulating immune cells. All specimens from NIH patients will be sent to the lab of Dr. Fran Hakim in Building 10/CRC, Room 12C216, 10 Center Drive, Bethesda MD 20892 (301 402-3627) for initial processing. The samples to be utilized for leukotriene levels will be then sent to the Core Endocrine Laboratory in frozen batches. For FHCRC patients, samples may be processed and sent to Dr. Fran Hakim for subsequent distribution and analysis as in Appendix 2b.

- Leukotriene levels in Bronchoalveloar lavage fluid (Required for adult patients, optional for pediatric patients): Fluid from the bronchoalveolar lavage will be sent to the laboratory to evaluate for infectious diseases; any remaining BAL fluid after essential tests will be requested for analysis of leukotriene receptor levels on immune cells. This

will be performed by Dr. Hakim's laboratory Building 10, Room 12C216, 10 Center Drive, Bethesda MD 20892 (301 402-3627). For FHCRC, BAL is not required, but if obtained samples will be processed as in Appendix 2b.

- Quality of Life (QOL) and Functional Assessment: Patient-reported functional status will be measured using the Human Activity Profile (HAP) questionnaire (for adults over the age of 18) (Appendix 9) and the Activities Scale for kids (ASK) questionnaire (for children up to 18 years of age). Quality of life assessment will be conducted using the VARNI for subjects aged 5-18 years and by SF-36 (version 2) and the FACIT-G, FACT-BMT for those greater than 18 years of age. [34-38] Lee Symptom scale, cGVHD self report, and Ocular Surface Disease Index (OSDI) will also be done at baseline and follow-up time points (Appendices 10 and 13).

- Leukopheresis (Optional): Subjects at NIH will have the opportunity to consent to, or decline, a leukopheresis at the start and conclusion of the study for research purposes. For patients who consent to this procedure, a one pass leukopheresis will be performed by the Department of Transfusion Medicine at NIH. Only patients with sufficient bilateral peripheral access will be eligible for this procedure. Approximately 2-5 liters of blood will be processed with a target of 2×10^9 cells obtained for research immunologic studies. Leukopheresis will not be performed at FHCRC.

- BAL: For patients greater than 18 years of age, a bronchoalveolar lavage will be performed. BAL fluid will be used to screen for infections and for research purposes, if one has not been performed within the last 3 months. Positive BAL results will be addressed as follows: 1) if the patient has signs and symptoms of active infection, or the result is likely to reflect active disease, the patient will initiate anti-microbial therapy with resolution of symptoms prior to the start of study drug, 2) if the organism is deemed most likely to be a colonization given the clinical picture, it is the discretion of the institutional PI or AI to determine if increased prophylaxis is necessary. This may be initiated coincident with study drug. Research studies on the fluid will include analysis of cell populations if possible. For FHCRC, BAL is not required unless clinically indicated, but if obtained, samples will be processed as in Appendix 2b and will be performed per institutional guidelines at NIH or FHCRC. (The risks of this procedure are discussed under section 6.3.3).

3.4.2 Patients will be evaluated by a health care provider every cycle for the duration of the study period (cycles 1-6) to include:

- History and physical examination, and respiratory evaluation including oxygen requirement.
- Laboratory assessment: Liver panel.

3.4.3 On Study Evaluation: Evaluations must be conducted at one of the 2 cooperating institutions: National Institutes of Health or Fred Hutchinson Cancer Research Center. For any patient receiving extracorporeal photopheresis, every attempt should be made to obtain all blood laboratory studies just prior to photopheresis therapy to minimize the contribution of pheresis

to blood analyses. A 2 week extension will be allowed at any endpoint evaluation if a subjects clinical picture would preclude the study evaluation (e.g. patient is admitted to the hospital with pneumonia). History and physical examination will be once during each drug cycle and periodically at follow-ups (baseline, during cycles 1-6, 6 months post-protocol therapy, and 18 months post-protocol therapy). Any side effects (including but not limited to: sleep disturbances, allergy symptoms, and rash) must be recorded. At the baseline, 3 month, 6 month, 6 months post-therapy and 18 months post-therapy, physical examination must include an assessment of each of the recorded graft versus host disease manifestations (with NIH consensus GVHD documents completed, Appendix 4 and 6). In addition, detailed pulmonary assessment must be recorded including oxygenation (with and without oxygen if the patient is on oxygen), respiratory rate at rest, character of lung sounds (rales, rhonchi, crackles, focal or diffuse, air exchange). A 2- and 6-minute walking test of pulmonary endurance must be conducted (per institutional guidelines) and recorded at each visit.

- Concurrent Medications must be documented to include all medications administered in the intervening time frame since the last on-study evaluation.

- Laboratory studies must include the following (baseline, after 3 cycles, 6 cycles, 6 months post-protocol therapy, and 18 months post-protocol therapy):
  Complete blood counts with differential.
  Complete chemistry panel: sodium, potassium, chloride, CO2, blood urea nitrogen, creatinine, calcium, phosphorus, and magnesium.
  Liver panel: ALT, AST, total and direct bilirubin.
  HIV and HCV PCR (only for the baseline time point at NIH).

- Pulmonary Function Tests (PFTs) (baseline, after 1,2,3 and 6 cycles, 6 months post-protocol therapy, and 18 months post-protocol therapy): for all patients greater than 6 years of age. FEV1, FEV1/FEV ratio, FEF 25-75, and DLC02 must be recorded. Also, patients should have a pre and post bronchodilator evaluation. Pulmonary function will be expressed as a % of predicted for age for adults and by size for children. PFTs at the 1,2, and 3 month timeframes may be performed at non-accruing sites. PFTs at the baseline and 6 month time points must be performed at the accruing site. Baseline, 3 and 6 month on study, and 6 month and 18 months post study drug PFT's (DLCO) will be adjusted for hemoglobin. Baseline PFT's will be repeated if the patient presents with signs and symptoms of an active infection after obtaining PFTs.

- Leukotriene production studies (baseline and after 3rd and 6th cycles): Blood and urine will be collected to measure leukotriene levels (Cysteinyl and LTB4). BAL fluid, to be obtained only if clinically indicated, will also be collected to measure leukotriene levels, after microbiologic samples have been sent. Blood will also be processed for multiparameter flow cytometry to measure leukotriene receptor levels on circulating immune cells. Please see Appendix 2b for processing information. For FHCRC, BAL is not required, but if obtained, samples will be processed as in Appendix 2b.

- Radiographic Evaluation (baseline and after 6 cycles, 6 months post-protocol therapy NIH only, and 18 months post-protocol therapy NIH only): All patients must have a high resolution, expiratory chest CT (supine). Patients at FHCRC may elect not to perform the

6 months post-protocol therapy and 18 months post-protocol therapy if not clinically indicated.

- Quality of Life and Functional Assessments (baseline and after 6 cycles, 3 months post-protocol therapy, 6 months post-protocol therapy, and 18 months post-protocol therapy). If any of these tests have been done within the past 7 days for other NCI protocols to include: NCI Protocol 04-C0281 or IRB-approved FHCRC studies, these may be used for this study's endpoints.

- Documentation of Compliance: During the study period (first 6 cycles), patient compliance must be documented. This may include either: collection of patient diaries (filled in by patient during the study period), documentation of phone call during or after study period, and/or documentation within visit note at follow-up.

3.4.4 **Biologic Studies:** Research blood aliquots will be minimized for pediatric patients <10 years of age or < 30kg to minimize phlebotomy risk. The total aliquot of phlebotomy will not exceed 3 mL/kg per draw and 7 ml/kg in a 4 week period for research studies. Should the research requests exceed these restrictions, research studies will be done in the order of Appendix 2b. For information on ETIB collection handling of specimens, see Appendix 14.

3.4.4.1 Studies to elucidate the pathogenesis of bronchiolitis obliterans to include multiparameter flow cytometry analysis and serum analysis of relevant cytokines.

3.4.4.2 Background: Little is known regarding the pathogenesis of BO or other cGVHD manifestations following stem cell transplant. In part, this is due to the lack of good animal models. As a result, human immunologic studies in this patient population are invaluable to obtain insight into the pathogenesis of disease. Studies have correlated poor thymic function with cGVHD [39-41] possibly implicating alloimmune peripherally expanded T cells in the cGVHD process. Additionally, there is emerging data that aberrant B cells [42], eosinophils [23], and monocytes [43] may contribute to the genesis and maintenance of the alloreactive cGVHD environment. Since leukotriene receptors are upregulated on these immune cells (monocytes, eosinophils, B and T cells) in the presence leukotriene production and cell activation, and since leukotriene production has been associated with lung inflammation, identifying activated cells with leukotriene receptor upregulation in BO may provide clues to the pathogenesis of BO after BMT. Finally, cytokines involved in the maintenance of activated lymphocyte subsets will be measured to substantiate hypotheses suggestive of particular cellular contributions to cGVHD (to include IL7 that activates naïve T cells and B cells, IL15 that activates NK cells and memory CD8+ T cells, and IL21 that has been linked to B and T cell autoimmunity.)

3.4.4.3 Objectives/Specific Aims:

1. Determine the expression of leukotriene receptors on circulating immune cells (including T cells, B cells, eosinophils, neutrophils, and monocytes) before montelukast administration and after therapy using flow cytometry. These will be correlated with the leukotriene levels.

2. Determine cytokine levels of those cytokines relevant to lymphocyte activation and sustenance (IL7, IL15, IL21) using immunofluorescent techniques to evaluate if these are elevated in BO and if montelukast leads to a reduction in these cytokines.

3. Enumerate activated cellular subsets in patients pre- and post- montelukast therapy to determine the cells involved and if montelukast affects these populations. As part of this effort, these profiles will be compared to determine if there is a group of patients likely to be more responsive to the introduction of montelukast for the design of future studies.

3.4.4.4 Methodology: The following studies will be performed on peripheral blood and aphersis (if available) samples. Blood samples (20 cc in red/green CPT herapin tubes, age adjusted for weight in pediatric patients) will be drawn for evaluations. Time points will include: 1) pre-study, 2) 3 months into therapy, 3) at the conclusion of the study at 6 months. Complete blood counts will be collected on the same day. Samples should be delivered to the lab of Dr. Fran Hakim in Building 10, Room 12C216, 10 Center Drive, Bethesda MD 20892 (301 402-3627) (refer to appendix 14, 2b).

1. Peripheral blood: quantity (50 mL). Flow cytometry will be performed on peripheral blood and apheresis (if available) samples. Commercially available antibodies to BLT1 receptor and CysLT receptor 1 would be utilized with concomitant staining to identify the immune cells infiltrating the lung tissue (including CD4+ and CD8+ T cells, CD19+ B cells, CD14+ monocytes and macrophages, neutrophils, eosinophils). A T/B/NK panel will be performed simultaneously for cell count correlations with research labs.

2. Plasma (5 mL). Plasma will be spun in refrigerated centrifuge and frozen immediately. For leukotriene studies, 3 ml total (from an EDTA tube) will be stored at NCI and subsequently utilized for cytokine studies using immunofluorescent technique. Plasma from normal donors will be used as a comparison.

3. Urine: quantity (50 mL). Two 25 mL aliquots of 24 hour urine collection will be frozen and stored at NCI, laboratory of Dr. Fran Hakim, head of the pre-clinical core.

4. Tissue (optional): Lung biopsy specimens diagnostic for bronchiolitis obliterans will be sent to NCI for pathologic review if available. Should there be extra paraffin embedded lung tissue from prior biopsies, leukotriene receptor and enzyme levels will be tested using immunohistochemistry technique.

5. BAL fluid (adult patients): For patients who undergo bronchoalveolar lavage, excess fluid not needed for the clinical indication will be sent to the laboratory of Dr. Hakim at NCI (301 402 3627) for immune cellular studies.

3.5 Concurrent Therapy for Chronic Graft versus Host Disease:

As part of the study design, patients may currently be taking medications targeted to treat both bronchiolitis obliterans and/or other manifestations of chronic GVHD. Since patients are required to demonstrate lack of improvement in BO within a minimum of 3 months on these agents prior to enrollment, the effects observed on this protocol will be attributed to montelukast. Patients may experience improvements in other aspects of cGVHD prior to enrollment; these patients are eligible as long as their FEV1 does not improve, signifying stable or worsening BO. Most protocols demonstrate improvement in BO within a 3 month time frame from agents including immunosuppressants and steroids. Furthermore, these agents have not shown consistent and long term benefit for patients with BO after BMT, thus greater exposure to these agents is unlikely to lead to a benefit (please see 1.2.1). During protocol therapy, patients will be maintained on their enrolling cGVHD therapeutics as much as possible with medications as detailed below.

3.5.1 **Non-steroid therapy:** Patients meeting entry criteria receiving therapy for chronic graft versus host disease in the form of approved immunosuppressant medications or extracorporeal photopheresis (ECP) will be expected to continue these therapies at the same level of therapy for the treatment of BO for the first six months of the study (until the primary endpoint is met) with the exception of steroids. Patients may have up to a three week interruption in ECP therapy due to the occasional timing barriers to receiving this therapy (e.g. center closed for holiday). For patients on ECP therapy, samples for study evaluations must be collected just prior to ECP therapy. Patients receiving immunosuppressants with narrow therapeutic windows requiring monitoring (e.g. sirolimus) should continue these medications within the same therapeutic window as the 3 months prior to enrollment. Dosage adjustment in these medications to maintain a patient within this therapeutic window is expected and not a breach of protocol. However, discontinuation or initiation of new systemic therapies for BO during the protocol meets criteria for withdrawal from the study during the first six months of study evaluation. Every attempt should be made to minimize changes to the cGVHD immunosuppression regimen. However, given the severity of cGVHD in this population and the potential need for new therapies for another manifestation of cGVHD, other systemic therapies or escalation in therapy will be permitted for these non-BO manifestations. These will be documented in the patient record and included in the summary analysis as potential contributors to any improvements seen in these patients on study. Patients should not discontinue chronic GVHD therapies during the first six months of the protocol with the exception of patients who have toxicities due to current GVHD therapies. Patients may discontinue or substitute a similar medication due to toxicity.

3.5.2 **Steroid therapy:** For patients on greater than physiologic dose steroids, a steroid taper may begin 8 weeks after starting montelukast therapy if the study physician deems this medically appropriate or if unacceptable toxicity to this medication occurs. Baring toxicity, patients will taper no faster than the following schedule: 10% of starting dose decrease per week for the remaining 16 weeks of the study until the primary endpoint of the study is reached. (For example, a patient who starts a steroid taper at month 5 of the study protocol will be tapered no faster than 10% per week and thus will finish the primary end point of study at no lower than 40% less than the entry dose). Should patients reach physiologic dosing (by age/ weight), the taper will cease until after the six month primary endpoint. Local steroid therapy to include inhaled steroids may be initiated during this period and should be recorded as a concurrent medication. Should worsening symptoms of cGVHD occur during the

steroid taper, these must be recorded, and steroid burst is permitted during the study. This also must be documented including the dose (expected to be 1-2 mg/kg for 5-7 days). Steroid pulses need to be reviewed by local PI or LAI approval. These will be included in an exploratory analysis to evaluate if pulmonary function improves following this steroid escalation. However, published data would not suggest that improvement is likely in this setting.

3.5.3 **Infectious disease prophylaxis** as outlined in section 4.1. Initiation of infectious disease agents to treat or prophylax against infections while on study is not a breach of protocol. However, life-threatening infections should require contact of institutional PI or LAI, and patients should discontinue montelukast in this setting.

3.5.4 **Contraindicated therapies:** Contraindicated therapies include those that interfere with the metabolism or action of montelukast. Rifampin and Phenobarbital are contraindicated with montelukast therapy as these have been shown to alter the drug metabolism. Greater than one age-appropriate dose per day of aspirin and cyclo-oxygenase inhibitors (including ibuprofen NSAID products) are contraindicated as these can interfere with the action of montelukast, potentially driving leukotriene production by inhibiting an alternate pathway of arachidonic acid breakdown. We have set the upper limit for daily doses to 325mg/day of aspirin and no more than 1200mg/day of ibuprophen.

3.5.5 **Montelukast therapy**: After a patient is off-protocol therapy, he/she may elect to continue on montelukast. If this is the case, the primary provider/referring physician will generate a prescription for montelukast. At this time, montelukast will become a concurrent medication.

3.6 Criteria for Removal from Protocol Therapy and Off Study Criteria:

3.6.1 Criteria for Removal from Protocol Therapy:

1) Any patient with persistent grade 3 LFT toxicity (1 month after drug withdrawal) attributable to montelukast will be taken off treatment. However, patients who experience grade 3 toxicity due to some other manifestation of their cGVHD, but show improvement in their BO, will not necessarily be taken off montelukast.
2) Any patient with worsening pulmonary function as determined by two measurements greater than 2 weeks apart documenting greater than 15% absolute decrease in percent predicted FEV-1 on pulmonary function test while on study will be withdrawn from the study. (For example, if the patient's entry FEV-1 is 50%, a FEV-1 of < 35% of predicted will be considered a decline.)
3) Any patient with a life-threatening infection will be withdrawn from study after montelukast discontinuation.
4) Any patient with an unacceptable toxicity (as defined in section 3.3) attributable to montelukast will be taken off drug but continued on study.

5) Recurrent malignancy or necessity to start new systemic therapies for BO will also be an indication for study withdrawal after discussion with PI or LAI.
6) Use of contraindicated medications for the first six months of therapy including: new systemic therapies for BO, b) greater than one age-appropriate dose of ibuprofen or aspirin containing products that inhibit cyclooxygenase per day, and c) the introduction of rifampin or phenobarbital (for the duration of montelukast therapy).
7) Patients requesting to be removed from protocol therapy for any reason will be withdrawn.
8) Any patient who the PI determines is unable to comply with the protocol as outlined, for example, exhibits noncompliance with the protocol medication, follow-up appointments, or has an underlying medical condition that prohibits the completion of the protocol.
9) All patients at the completion of 6 cycles of therapy will come off-protocol therapy. Patients may elect to continue montelukast at the discretion of their referring physician; montelukast would then become a concurrent medication.

Patients who are off protocol therapy are to be followed until they meet criteria for Off-Study or the completion of the study.

3.6.2 Off Study Criteria

1) Inability to comply with study requirements will be sufficient reason to come off-study.
2) Death
3) Lost to follow-up
4) Withdrawal of consent for any further data submission.
5) Completed the 18 months post-cycle 6 follow-up.
6) PI decision to end this study

CRO will be notified by enrolling protocol research nurse when any patient is withdrawn from the study.

3.6.3 Off Study Procedure at NCI

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://camp.nci.nih.gov/ccr/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>.

3.6.4 Participating Site Off-Study Notification

All subjects must be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30 am to 5:30 pm EST Monday through Friday, excluding federal holidays. An off-study form will be supplied by the Coordinating Center, NCI CCR. Fax the completed off-study form to the CRO at 301-480-0757.

3.7 Off- Protocol Therapy, Off-Study, and Post-protocol therapy Evaluation (Appendix 2A)

The following studies should be completed at the time of study discontinuation (either at the time of off-study decision or at the conclusion of the protocol therapy).

3.7.1 Off-Protocol Therapy, Off-Study, or 6 months and 18 months after off-protocol therapy Evaluation

- -History and physical examination. Physical examination must be conducted by a study associate and must include an assessment of each of the recorded graft versus host disease manifestations. A 2-and 6-minute walking test of pulmonary endurance must be conducted and recorded at each visit. Oxygenation must be recorded, with and without supplementary oxygen if appropriate.
- Concurrent Medications must be documented to include all medications administered in the intervening time frame since the last on-study evaluation.
- Laboratory studies must include the following:
  Complete blood counts with differential.
  Complete chemistry panel: sodium, potassium, chloride, CO2, blood urea nitrogen, creatinine, calcium, phosphorus, and magnesium.
  Liver panel: ALT, AST, total and direct bilirubin.
- Immunologic screening: Immunoglobulin levels (IgG, IgE, IgA, IgM) CD4/CD8 total numbers and ratio (NIH lymphocyte TBNK). These tests will be sent to NIH for processing. Dr. Hakim's laboratory Building 10, Room 12C216, 10 Center Drive, Bethesda MD 20892 (301 402-3627).
- Pulmonary Function Tests (PFTs): for all patients greater than 6 years of age. FEV1, FEV1/FEV ratio, FEF25-75, and DLC02 (adults only) should be recorded. Also, patients should have a pre and post bronchodilator evaluation. Pulmonary function will be expressed as a % of predicted for age for adults and by size for children.
- Leukotriene production studies: Blood and urine will be collected to measure leukotriene levels (Cysteinyl and LTB4). All specimens will be sent to Dr. Hakim's lab (appendix 2b). Blood will also be processed for multiparameter flow cytometry to measure leukotriene receptor levels on circulating immune cells.
- Radiographic Evaluation: All patients must have a high resolution chest CT at NIH. Patients at FHCRC will only perform the 6 months primary end point CT.
- Quality of Life and Functional Assessments.

4 SUPPORTIVE CARE GUIDELINES

Supportive care will include continuation of all prior therapies for graft versus host disease at stable doses. Stress dose steroids may be given as clinically necessary. However, no new therapies should be instituted for the duration of the study. Patients will be instructed not to take additional medications (including over the counter medications) during the study without consultation of a study investigator. If a new therapy is necessary for any indication, this should be recorded in the record. Greater than one age-appropriate dose of ibuprofen or aspirin is contraindicated in all patients during study evaluation (the first 6 months). Additionally, rifampin and Phenobarbital affect the metabolism of montelukast and therefore should never be administered with montelukast.

Appropriate infectious prophylaxis (to include pneumocystis prophylaxis and penicillin prophylaxis) or treatment must be administered during the study. Patients receiving greater than 1 mg/kg of steroids should be on anti-mould prophylaxis as per the following table (http://intranet.cc.nih.gov/bmt/_pdf/table_VI.pdf). For questions, investigators should refer to the NIH Allogeneic Stem Cell Transplantation guidelines (http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml). Appropriate surveillance should be continued for the duration of the study including CMV surveillance (in CMV seropositive patients and/or donors), weekly blood culture surveillance for patients on high dose steroids, and other studies as deemed clinically appropriate by the referring physician.

Hematologic support may be given as deemed clinically appropriate and must be documented.

Other supportive care to include: nutritional support, physical therapy, occupational therapy, psychosocial therapy as deemed clinically appropriate.

5 DATA COLLECTION AND EVALUATION

5.1 Data Collection

Data will be prospectively collected at all 4 institutions (after Institutional Review Board approval) and subsequently entered the Cancer Central Clinical Data System Database (NCI C3D; information at http://ccrtrials.nci.nih.gov). After obtaining Informed Consent, a file will be created in the database with standardized forms. The research database will maintain data for described endpoints in the protocol. The medical record will maintain complete records on each patient including any pertinent supplementary information obtained from outside laboratories, outside hospitals, radiology reports, laboratory reports, or other patient records. The NCI C3D will serve as the primary material from which all research analyses will be performed. The primary documentation will include: a completed patient eligibility check list, patient history, flow sheets, specialty forms for pathology, radiation, an off-study summary sheet, including a final assessment by the treating physician.

5.1.1 **Eligibility Checklist:** To be completed at study entry and forwarded to the protocol research nurse.

5.1.2 QOL Assessment Forms: (Appendix 13).

1) Adult patients: QOL for patients greater than 18 years of age will be given at all participating institutions.
2) Pediatric Patients: Quality of life self assessment using the VARNI will by administered to transplant recipients less than 18 years of age at all participating institutions.

5.1.3 **Protocol Deviations**/Unanticipated problems (UPs): Any protocol deviations or UPs should be directly reported to the PI, PC, or AI. These deviations and UPs will be reported to each site's respective IRB. The outside institutions are required to send all protocol deviations and UPs to the PI to be submitted to the NCI IRB.

5.1.4 **Confidentiality Protection**: Prior to analysis, all identifiers will be removed and a random number ascribed to protect patient confidentiality.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. 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 and, 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.

5.2 Response Criteria:

5.2.1 Evaluation of Pulmonary Response

There are 2 primary endpoints of this study. The first is stabilization or improvement of the absolute change of FEV-1 percentage predicted after 6 cycles (of 30 days) of continuous montelukast administration (completing study duration) using the baseline and 6th cycle PFT measurements. Exploratory analyses will also compare FEV-1 responses at subsequent trial endpoints including: 12 and 24 months. In addition, exploratory analyses will also compare FEV-1 responses in patients with biopsy-proven BO in comparison to those who met clinical criteria for study entry if sufficient numbers permit. Secondly, the change in absolute FEV-1 will also be computed as a change in slope to explore if patients who had a decrease or stable slope at the conclusion of the study as compared to the slope at study entry (either for diagnosis of BO or the FEV-1 change over 3 month pre-enrollment period on current cGVHD regimen). This has been done in one prior study of lung transplant related BO.[44] Pulmonary response will be evaluated in secondary endpoints as well. These will include: oxygen saturation/requirement, other parameters of pulmonary function tests including: FEF25-75, RV, DLCO2 (adults only), and the ratio of FEV1/FVC and FEV1/SVC, and 2 and 6 minute walk times.

5.2.1.1 Primary Endpoint Evaluation (FEV-1)

Responsive disease (RD): will be defined as $\geq$ 15% absolute improvement in the percentage predicted FEV-1. (For example, a patient with a baseline FEV-1 of 30% predicted would need to achieve a 6 month FEV-1 of 45% of predicted to be considered responsive disease). RD for the slope of FEV-1 change will be an increase in the slope of absolute FEV-1.

Progressive disease (PD): will be defined as > 15% decrease in FEV-1 documented on 2 PFT evaluations greater than 2 weeks apart. PD for the slope of FEV-1 change will be a decrease in the slope of absolute FEV-1.

Stable disease (SD): will be defined as < 15% change in the absolute FEV-1. Stable disease for the slope of FEV-1 change will be a 0 change in FEV-1 slope.

FEV1 values have been used extensively in the literature to indicate improvement, stabilization, or decline in lung function in this population.[2, 10, 45] Furthermore, the rate of FEV1 decline has been significantly associated with survival in patients with air flow obstruction following BMT.[1] Unfortunately, some studies do not state the criteria to designate FEV1 improvement or decline.[10, 45] Others considered 5% or 10% change in FEV1 significant.[1, 2] To record a PFT value according to current guidelines for PFT testing, the patient must do the test twice and generate values no more than 10% apart.[46] Thus, given that the change of 10% could be due to test-to-test variability, this study will use 15% or greater for a change of clinical significance. This cutoff value for FEV-1 significance is further supported by recommendations of both the American Thoracic Society and European Respiratory Society that have designated that FEV1 values are the most reproducible measurements of lung disease and that FEV1 values accrued greater than 1 week apart should use a change of greater than 12% to determine significant improvement or decline. [47] Thus, for the purposes of this trial, 15% absolute change will be required to designate that a clinically significant change in lung function parameters has occurred.

5.2.1.2 Secondary Endpoints to Evaluate Pulmonary Function

Oxygen saturation and supplementation: oxygen saturation will be recorded at rest at study entry and at subsequent intervals throughout the study. Improvements in oxygen saturation will be considered for patients with a baseline oxygen saturation < 90% who have an increase in the absolute value of ≥5%. Oxygen requirement will also be recorded at study entry. Any decrease in oxygen requirement (day or night) will be considered a response as long as baseline oxygen saturation is maintained on the new setting.

FEF25-75, RV or RV/FVC, DLCO2 (adults only), and ratio FEV1/FVC and FEV1/SVC: For FEF 25-75, DLCO2 (adults only), and the ratio of FEV1/FVC and FEV1/SVC, the same criteria of RD, PD, and SD will be utilized as for FEV-1. For FEF25-75 and the ratio FEV1/FVC and FEV1/SVC, baseline impairment is: < 20% of predicted for FEF25-75 and FEV1/FVC and FEV1/SVC. For DLCO2, a baseline impairment is defined as a decrease DLCO2 of at least 25% (e.g. decrease from 20 to 15 ml/min/mmHg CO) as has been used by other studies of lung function post-BMT.[4] For RV/FVC or RV, ≥120% baseline value is evidence of obstruction. A decrease below 120% will signify response, any value > 120% is non-responsive disease. In addition, the lung function score (LFS) will be calculated from these data and compared as an absolute value between study entry and the 6 cycle, 6 and 18 months post-protocol therapy data points (see appendix 8).

Pulmonary Endurance (2 and 6 minute walk time): Walk time at 6 minutes will be compared to age-matched normal values for adults and children [48, 49]. Two minute walk time results will be incorporated as recommended in the current consensus guidelines for cGVHD studies [29] based on reliability data demonstrated in patients with similar obstructive lung disease processes [50].

5.2.1.3 Evaluation of the Impact of Montelukast on Leukotriene Production

Leukotriene levels and leukotriene receptor expression on immune cells: These will be reported as absolute values for the leukotriene levels and compared to the Core Endocrine Laboratory normal values. Data will be reported both as an absolute change per patient. Leukotriene receptor expression will be reported as a percentage on tested immune cells. These will be included in exploratory analyses. Any changes will be compared with other parameters of lung function in the primary and secondary endpoints to evaluate if there is a correlation between decreased leukotriene production and improved lung function in BO after BMT.

5.2.1.4 Evaluation of the Impact of Montelukast on other cGVHD Processes

Chronic GVHD manifestations: Chronic GVHD manifestations will be evaluated using the guidelines established by the chronic GVHD consortium (see Appendix 4-13). Quality of life and function parameters will be explored in this evaluation as well to determine if montelukast impacts these parameters.

5.2.1.5 Impact of Montelukast on Overall 2 year Survival

2 year Overall Survival: Two year survival will be recorded and compared to historical controls. For historical controls, the patients from the two largest publications on BO after BMT to date were combined and the approximate 2 year overall survival calculated to be approximately 43%. [2, 51] Thus, 40% will be used as the baseline 2 year overall survival.

5.3 Toxicity Criteria

Adverse events on this study will be reported using the NCI mechanism of NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov) under reporting guidelines. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0.

An adverse event will be defined as any new, concerning medical condition or worsening of a previously existing medical condition.

5.4 Statistical Considerations

5.4.1 Subject Accrual

Non-pregnant female and male subjects from all racial and ethnic groups are eligible for this trial if they meet entry criteria. Data suggest that montelukast has equivalent activity across racial, ethnic and gender groups.[52] Although every effort will be made to incorporate individuals representative of the national population with chronic GVHD, issues of limited accrual and the desire to restrict the number of individuals exposed to this therapy with as yet undetermined benefits may not permit this study to explore the impact of race or gender. Should the analysis suggest that there is a difference

observed across race or gender, accrual may be expanded or additional studies designed to address these questions.

5.4.2 Statistics and Feasibility

The primary objective of this trial is to conduct a phase II study to determine if the use of montelukast is able to result in improvement or stabilization of bronchiolitis obliterans (BO) in patients with this condition as part of cGVHD resulting from marrow transplantation. Additionally, this study will aim to determine if montelukast lowers leukotriene levels in these patients to gather data regarding the genesis of bronchiolitis obliterans after BMT.

The primary analysis for improvement in pulmonary function will be the percentage change in the PFT-derived percent predicted FEV-1 from the conclusion of therapy as compared to the baseline at study entry (with 6 cycles of 30 days of continuous therapy). Patients enrolled on the study will have a diagnosis of BO, but the severity of lung disease can vary substantially. Patients are classified according to the following scale[28]: mild whereby FEV1=60-79%, moderate FEV1=50-59%, and severe FEV1$\leq$ 49%.

Disease stabilization or improvement will be noted if the patient's FEV-1 does not decline by greater than an absolute change of 15% of predicted FEV-1 over a 6 cycle period, while a decline of greater than 15% will be considered to be a progression. For example, if the patient's entry FEV-1is 50%, only a value in excess of 65% of predicted would be considered an objective improvement while a value of 35% of predicted will be considered a decline.

For purposes of this phase II study, all enrolled patients will be considered together as one group, and the overall goal will be two-fold. First, this study is designed to determine if the proportion of patients with improvement or stabilization of disease is able to be as high as 80% instead of 60%, which may be inferred from the collective data obtained from the published BO literature [2, 10, 31, 32] as the percentage who have this level of benefit using standard of care treatments. Secondly, this study is designed to identify if montelukast leads to an improvement in the slope of absolute FEV-1 values, that is, whether this difference in slopes after use of the agent compared to before the agent is positive, and not equal to 0. For this analysis, each patient serves as his/her own control and will be placed in a subset of patients who either have stable or an altered rate of fall in FEV-1 values.

A sample size of 45 total evaluable subjects will be enrolled based on the following criteria:

1. Using an exact binomial test with a two-sided 0.05 alpha level, nQuery advisor indicates that 45 total patients would be sufficient to have 82% power to detect if the true degree of benefit would be improvement or stabilization in 80% of patients as opposed to 60%.

2. With 45 patients, a paired t-test with a 0.05 two-sided significance level will have 90% power to detect a 0.5 SD effect size, that is, whether the paired difference in slopes pre-treatment vs. post-treatment differ from zero. The slopes will be formed by linear regression through all available pre-treatment FEV-1 values and then separately through the post-initiation of treatment FEV-1 values. If the difference in these slopes is not normally distributed ($p< 0.05$ by Shapiro-Wilks test), then a Wilcoxon signed rank test will be used.

With 45 total patients, if the agent was able to show stable or improving disease in greater than 60% of patients, and be consistent with 80% showing improvement or stability, at least 34 of 45 patients would be expected to exhibit stable or improving disease. This is because 34/45 has an associated exact two-sided 95% confidence interval ranging from 60 to 87%.

Within individual severity groups, depending on the number of patients we are able to enroll, the percentage of patients who show improvement or stabilization may be able to be estimated as well, with reasonable precision.

In addition, we will obtain leukotriene levels on patients at baseline and after 6 cycles of treatment, and we will perform exploratory analyses to try to determine if there are patterns or trends in the leukotriene levels that may be related to the extent of disease over time. These analyses will be done using non-parametric correlation analysis and will be interpreted in the context of secondary, exploratory analyses.

It is theoretically possible that some degree of improvement may occur without treatment. Since this is a phase II study to determine if any benefit is plausible in these patients, positive findings of the degree we would consider beneficial (consistent with 80% who are stable or improving by predicted FEV-1 measurements or showing a non-0 difference between the pre-treatment and on/post treatment slope of benefit of FEV-1) would require more definitive confirmation in an appropriate randomized comparison in order to more accurately determination the degree of benefit in a definitive rather than phase II fashion. At this time, there is no viable control group to use in such a comparison; thus, we have to accept the small possibility of regression to the mean or possible changes in natural history as alternative explanations for any degree of improvement noted. However, it is anticipated that other arms for comparison may be available in the future, and they may be used in a later study if the results are promising from the present study.

It is also possible that the patients accrued in this study may have more severe disease than those represented in the published retrospective analyses. This will not pose a problem because we will be performing an analysis based on changes in slopes, with each patient as his own control.

Other outcome measures such as 2 and 6 minute walk test, scoring of infiltrates and pneumothoraces using CT scans of lungs [53], oxygen dependence, and quality of life questionnaires may also be used to evaluate the effectiveness of Montelukast in exploratory evaluations.

It is expected that up to three years may be required to enroll 45 patients who would be evaluated.

Patients unable to complete the primary study endpoints for reasons other than decline in pulmonary function necessitating withdrawal from study or toxicity from study drug will be replaced.
However, for patients who withdraw due to the toxicity of montelukast, worsening lung disease, or worsening systemic cGVHD manifestations, these will be included in the slope of

FEV-1 analysis and the line estimated with the FEV-1 values accrued before and during the study prior to withdrawal.

Toxicity of montelukast in this population will be evaluated in all patients. Because the previously performed pilot had 0 of 15 patients with toxicity attributable to montelukast (0%), in the present study, we will evaluate the toxicity due to montelukast in the first 20 patients, review toxicity data at this interim study point, and determine if the toxicity rate attributable to montelukast appears to be excessive.

5.5 Multi-Institutional Guidelines:

This is a multi-institutional trial with 2 co-operating institutions: Fred Hutchinson Cancer Research Center and National Institutes of Health, National Cancer Institute. Institutional review board (IRB) approval will be obtained from Fred Hutchinson Cancer Research Center after IRB approval is obtained by NCI.

5.5.1 IRB Approvals: All approved IRB documentation from outside sites will be forwarded to NCI IRB for review by the NCI PI. Annual review approvals will also be submitted to NCI IRB by the NCI PI as well. Registration for this trial will be suspended at any institution if a current IRB is not on file at NCI. The Coordinating PI (NCI PI) will ensure that no patient is entered onto the trial at a participating institution without full IRB approval of the study. Thus, the NCI IRB must approve the addition of each participating institution to the protocol; furthermore, a copy of the local IRB approval from each participating institution will be required before NCI IRB approval is granted.

5.5.2 Amendments and Consents: The PI will provide NIH IRB with any and all documentation of amendments, consents, and approvals from IRB reviews at all participating institutions. All amendments to the protocol or the NCI consent are to be approved by the NCI PI and the NCI IRB and then submitted to the participating institution's IRB for approval.

5.5.3 Data Collection and Toxicity Reporting: The NCI C3D data base will be utilized; data will only be collected at the time points specified in this trial. Participating sites will be trained in the use of C3D and directly enter data at these sites into C3D. Any questions or concerns should elicit immediate contact of the NCI PI or LAI. All serious adverse events from participating institutions must be submitted to NCI IRB within 7 days. Serious adverse events (SAEs) are defined in section 7.1.

5.5.4 Data and Center Audits: Yearly audits of IRB-approved participating institutions will be required and performed by NCI. Audits will include random evaluation of the participating institution patient's charts and review of the Standard Operating Procedures (SOP) at the

time of the visit. Data and appropriate source documentation from participating institutions should be available when the NCI audit occurs.

6 HUMAN SUBJECTS PROTECTIONS

6.1 Rationale for patient selection

All patients with bronchiolitis obliterans following allogeneic or autologous stem cell transplantation are eligible for this trial. All ethnic groups and both sexes may be enrolled. Ethnic enrollment may vary as ethnic groups afflicted by graft-versus-host disease symptoms may vary. This has been addressed in section 5.5.1. In addition, this trial is open to pediatric as well as adult patients. The purpose of this trial is to determine if montelukast ameliorates bronchiolitis obliterans in both pediatric (greater than 6 years of age) and adult populations. Pediatric patients less than 6 years of age will not be included due to the fact that these patients are unable to perform pulmonary function tests- the primary measure for the primary endpoint of this study. Pregnant females will be excluded from this trial due to unknown effects of montelukast on a fetus developing within a woman with cGVHD and BO. It is unlikely that our patient numbers will permit statistics of individual ethnic groups. However, the accrual may permit evaluation of pediatric versus adult bronchiolitis obliterans patients.

Patients will be recruited from the post-BMT populations at the four participating institutions, their affiliates, and from the NIH Protocol #04-C-0281 entitled: "Prospective Assessment of Clinical and Biological Factors Determining Outcomes in Patients with Chronic Graft-Versus-Host Disease."

6.2 Participation of Children

Patients eligible for the trial must be greater than 6 years of age in order to obtain accurate pulmonary function tests for monitoring purposes. Although the purpose of the trial are to determine if montelukast ameliorates bronchiolitis obliterans, there must be accurate measurements to ascertain that patients do not deteriorate on this new agent. Thus, only children who may perform accurate pulmonary function tests, i.e. greater than 6 years of age, will be eligible. Pediatric patients will be followed closely by a team of physicians, nurses, and social workers who have extensive experience working with children. All children enrolled on this study will be followed by the physicians of the Pediatric Oncology Branch, NIH or Fred Hutchinson Cancer Research Center.

6.3 NCI PARTICIPATION OF 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 **6.4**), 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.

6.4 Evaluation of Benefits and Risks/Discomforts:

6.4.1 **Montelukast:** The primary goal of this study is to determine if montelukast results in improvement or stabilization of pulmonary compromise due to BO following BMT. Montelukast has been well tolerated in over 2 million patients worldwide, of whom greater than 200,000 were children.[26] All patients will be closely monitored for evidence of adverse events while on study. This protocol provides minimal risk to pediatric and adult patients given the excellent toxicity profile of montelukast. However, patients will be closely monitored.

6.4.2 **Leukapheresis:** Leukapheresis will be performed only in the NIH Department of Transfusion Medicine and supervised by the experienced staff of the Blood Bank. This procedure has been utilized safely in this patient population for this indication. The patients will be closely monitored for side effects including possible bleeding, infection, thrombosis, and vascular perforation, and any adverse events recorded and immediately reported to the PI or LAI. Treatment for these adverse effects may include: decreasing the pace of the procedure, administering calcium supplements, giving additional blood products. Additionally, in the very rare event that an allergic reaction ensues, treatment may include giving antihistamines, intravenous fluid support, or epinephrine.

6.4.3 **Bronchoalveolar lavage:** Bronchoavleolar lavage will be performed in the Medical Intensive Care Unit by an experienced physician at NIH or a participating institution. BAL will not be done for research purposes only in those less than 18 years of age. The benefits of BAL include the diagnosis of pulmonary infections, which can complicate the diagnosis of BO or AFO in up to 10% of cases. Pulmonary infections in patients with chronic GVHD are often life-threatening. Complications of the BAL procedure are rare. The risks include: allergic reactions to the topical anesthetic, bronchospasm during the procedure, alterations in gas exchange, bleeding from the nasal mucosa, hoarseness, cardiac arrhythmias during the procedure, fever, sedation risks. Precautions will be taken to minimize these risks including: an intensive care environment equipped to handle allergic reactions with supportive care, bronchodilators available for bronchospasm, supplemental oxygen for gas exchange abnormalities, platelet check prior to procedure, and electrocardiographic monitoring during the procedure. With appropriate supportive care, most of these complications should resolve within 24 hours including: epistaxis, hoarseness, bronchospasm, allergic reactions, fever, and abnormalities in gas exchange.

6.5 Risk/Benefit Analysis

Patients are enrolled on this trial with an intent to treat a life-threatening, debilitating, progressive disease for which there is no consistently effective therapy. The treatment is a well-tolerated medication with a very low incidence of toxicity. Despite this, these patients will be closely monitored for toxicity. Excellent patient care will be considered paramount and study endpoints secondary to this goal. Data suggests that montelukast may benefit these patients. Additionally, the

careful clinical monitoring and care that they will receive by enrolling on this trial may provide added benefit as well. All efforts will be made to minimize risks to all patients enrolled on this study.

Patients may also benefit from the insight that this study provides into the pathogenesis of BO after BMT. Increasing our understanding of this disease process may permit us to: 1) identify a subset of patients who may respond to montelukast (using leukotriene levels) or 2) identify a mechanism of disease progression that could be targeted and halted through new therapeutics.

Since there is evidence to suggest that montelukast is well studied in children and provides minimal risk to children with the potential to benefit these patients, this study meets the criteria necessary for Federal requirements stipulated for minors as study patients (45CFR46.405).

6.6 Consent and Assent Process and Documentation

The possible risks and benefits of this trial will be explained in layman's terms for patients and guardians. For patients who elect to enroll, consent will be obtained. A signed consent must be obtained by patient or legal guardian prior to study entry. The PI or LAI, an Associate investigator, or an appropriate designee will answer all questions regarding this medication and the purpose of the trial prior to obtaining consent. This study will require that investigators obtain consent from only 1 parent. Because many children have traveled great distances to come to the NIH, it is an excessive burden to demand 2 parental consents. In addition, many minors in the United States have only 1 parental guardian for medical decisions. Thus, this study requires the acceptance of the signature of either: 1) the sole primary decision maker for the patient, or 2) a single signature representing the consent of both parties. Both parties of joint consent will be contacted by phone to ascertain ascent of all guardians. Parents may give consent for children for whom they are guardians. All questions will be answered for pediatric patients in appropriate language. Verbal assent from the child will be accepted with parental guardian permission. All patients participating at NCI will sign NIH-2514-1 (Consent to participate in a Clinical Research Study) in addition to the protocol consent forms. Participating institutions will follow local IRB/institutional procedures for obtaining informed consent.

6.6.1 Telephone re-consent procedure

Re-consent 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.

6.6.2 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, 45 CFR 46.117 (b) (2) and 21 CFR 50.27 (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.

7 SAFETY REPORTING REQUIREMENTS 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.
All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

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 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 Coordinating Center PI, 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 greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.11 Determination of the causal relationship between the study medication and an adverse event will be as follows:

- Unrelated: AE clearly due to extraneous causes (e.g., underlying disease).
- Unlikely (must have 2 of the following): The adverse event: (1) does not have temporal relationship to intervention; (2) could readily have been produced by the subject's clinical state; (3) could have been due to environmental or other interventions; (4) does not follow known pattern of response to intervention; (5) does not reappear or worsen with reintroduction of intervention.
- Possible (must have 2 of the following): The adverse event: (1) has a reasonable temporal relationship to intervention; (2) could not readily have been produced by the subject's clinical state; (3) could not readily have been due to environmental or other interventions; (4) follows a known pattern of response to intervention.
- Probable (must have 3 of the following): The adverse event: (1) has a reasonable temporal relationship to intervention; (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions; (3) follows a known pattern of response to intervention; (4) disappears or decreases with reduction in dose or cessation of intervention.
- Definite (must have all 4 of the following): The adverse event: (1) has a reasonable temporal relationship to intervention; (2) could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions; (3) follows a known pattern of response to intervention; (4) disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure.

7.2 NCI-IRB and NCI Clinical Director Reporting

7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

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

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

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

7.2.3 All grade 3 and 4 (CTCAE) events that are not in the informed consent and that are possibly, probably, or definitely related to the research study are considered SAEs. However, the following expected complications from cGVHD are **exempt** and do not require SAE reporting:

- Blood count abnormalities (grade 3-4): Low CD4 count, iron overload, leukopenia, lymphopenia
- Dermatology (grade 3-4): nail changes, GVHD rash (to include scleroderma, lichenoid changes, hyper- or hypo-pigmentation, dry skin and alopecia) or cushingoid appearance due to steroid therapy.
- Gastrointestinal (grade 3): oral ulcers, anorexia, GVHD colitis, GVHD- associated diarrhea, zerostomia, nausea, salivary gland changes.
- Growth and Development (grade 3-4): avascular necrosis, growth velocity, delayed puberty.
- Musculoskeletal changes (grade 3-4): fracture, arthritis and fibrosis, osteoporosis
- Sexual Function (grade 3): erectile dysfunction, infertility, amenorrhea, vaginal stenosis, and vaginitis
- Events secondary to routine procedures performed for cGVHD therapies (grade 3-4): Extra-corporeal photopheresis, blood transfusions, PUVA therapy.

7.3 NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials

The site PI must immediately report to the coordinating center PI 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 within 48 hours of PI awareness of the event. The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

Please note that fillable version of a participating site problem form will be send it out upon request by Jennifer Hsu, RN. (See example as appendix 15)

7.4 Data and Safety Monitoring Plan

The clinical research team will meet on a regular basis when patients 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 patients.
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.
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.

7.4.1 **Protocol Monitoring Committees:** The NCI PI or LAI will have either a meeting or phone conversation with all IRB-approved participating institution PIs to discuss protocol progress on at least a monthly basis. In addition, the PI, LAI and protocol research nurse will provide continuous close monitoring with prompt reporting of serious adverse events to the IRB.

7.4.2 Sponsor Monitoring Plan

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. 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.
At least 25% of enrolled patients' will be randomly selected and monitored at least annually, based on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

7.4.3 Safety Monitoring Committee (SMC)

This protocol will require oversight from the Safety Monitoring Committee (SMC). Initial review will occur as soon as possible after the annual NCI-IRB continuing review date. Subsequently, each protocol will be reviewed as close to annually as the quarterly meeting schedule permits or more frequently as may be required by the SMC. For initial and subsequent reviews, protocols will not be reviewed if there is no accrual within the review period. Written outcome letters will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

7.5 Abnormal Laboratory Test Results

All clinically important abnormal test results will be appropriately followed up with further investigation and subsequent repeat tests at appropriate intervals until the value returns to baseline, an acceptable level, or a new diagnosis is made to justify a new baseline.

7.6 Withdrawal from Study

The reason for a patient withdrawal must be documented. Investigators will ascertain that there is adequate follow-up for patients for whom this is needed.

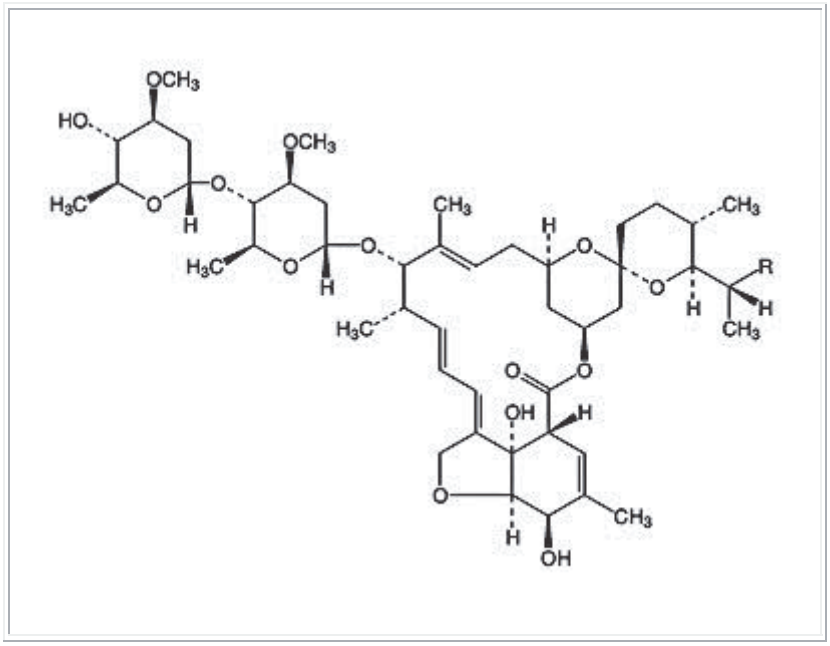
8 PHARMACEUTICAL DRUG INFORMATION

8.1 Montelukast (Singulair)

8.1.1 **Chemical name:** [R -(E)]-1-[[[1 - [3 - [2 - (7 - chloro-2 - quinolinyl)ethenyl]phenyl] - 3 - [2 - (1 - hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid, monosodium salt.

8.1.2 Molecular weight is: 608.18.

8.1.3 Chemical structure:



8.1.4 Commercial Formulation: Supplied as 5 mg chewable, and 10 mg tablets.

8.1.5 Storage: room temperature.

8.1.6 Stability: Montelukast remains stable when stored at 15-30 deg. Celcius. The product should be stored in the original container and restricted from light.

8.1.7 Route of administration: Oral. For adult patients, the oral tablet (10 mg) is easy to swallow. For pediatric patients, the oral tablet and packet is chewable and easy to tolerate.

8.1.8 Dose: Montelukast will be administered at appropriate dosage tablet 5 mg tablet nightly for children 6 to 14 years, and 10 mg tablet nightly for patients greater than 15 years as initial dose. For dose modifications, refer to section 3.2.

8.1.9 Drug Interactions: Rifampin and phenobarbital decrease the area under the curve of montelukast. Aspirin and NSAIDS that inhibit cycloxygenase are contraindicated as these may interfere with the mechanism of action of montelukast.

8.1.10 Known toxicities (see table below): Please utilize the table for the most accurate assessment of montelukast toxicities. The most common side effects in large trials include headache and fatigue. A toxicity table from Micromedix on Montelukast is included here:

8.1.11 ADVERSE REACTIONS

8.1.11.1 Adults and Adolescents 15 Years of Age and Older with Asthma

Montelukast (SINGULAIR) has been evaluated for safety in approximately 2600 adult and adolescent patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with **SINGULAIR** occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo, regardless of causality assessment:

Adverse Experiences Occurring in ≥1% of Patients with an Incidence Greater than that in Patients Treated with Placebo, Regardless of Causality Assessment		
	SINGULAIR 10 mg/day (%) (n=19 5)	Placebo (%) (n=1180)
Body As A Whole Asthenia/fatgue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.
Digestive System Disorders Dyspepsia	2.1	1.1
Gastroenteritis, infectious	1.5	0.5
Pain, dental	1.7	1.
Nervous System/Psychiatric Dizziness	1.9	1.4

Adverse Experiences Occurring in ≥1% of Patients with an Incidence Greater than that in Patients Treated with Placebo, Regardless of Causality Assessment		
Headache	18.4	18.1
Respiratory System Disorders Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/Skin Appendages Disorder Rash	1.6	1.2
Laboratory Adverse Experiences * ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9
1 *Number of patients tested (**SINGULAIR** and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.		

The frequency of less common adverse events was comparable between **SINGULAIR** and placebo.

Cumulatively, 569 patients were treated with **SINGULAIR** for at least 6 months, 480 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

Montelukast Side effects:

- Likely (occurring in greater than 20% of patients on montelukast drug studies): None reported
- Less Likely (occurring in greater than 2% and less than 20% of patients on montelukast drug studies): headache, abdominal pain, heartburn, cough, flu, increased liver function lab test
- Rare (occurring in less that 2% of patients on montelukast drug studies): fatigue, fever, nasal congestion, dizziness, abnormal urine test, agitation including aggressive behavior, allergic reactions (including swelling of the face, lips, tongue, and/or throat, which may cause trouble breathing or swallowing, hives and itching, and very rarely, chills, low blood pressure, fast heart rate, wheezing, difficulty breathing, and death), bad/vivid dreams, increased bleeding tendency, bruising, depression, diarrhea, drowsiness, hallucinations (seeing things that are not there), hepatitis (liver inflammation), indigestion, stomach infection, inflammation of the pancreas, irritability, joint pain, dental pain, muscle aches and muscle cramps, nausea, palpitations, pins and needles/numbness, restlessness, seizures (convulsions or fits), suicidal thoughts and actions, swelling, tremor, trouble sleeping, and vomiting.

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10 APPENDICES

10.1 Appendix 1: Performance Scales

%	Karnofsky†	Status	Lansky Scale#
100	Normal; no complaints/ no evidence of disease	**100**	Fully Active
90	Able to carry on normal activity; minor signs or symptoms of disease	**90**	Minor restrictions in physically strenuous play
80	Normal activity with effort; some signs or symptoms of disease	**80**	Restricted in strenuous play, tires more easily, otherwise active
70	Cares for self; unable to carry on normal activity or do active work	**70**	Both greater restrictions of and less time spent in active play
60	Requires occasional assistance but is able to care for most of his needs	**60**	Ambulatory up to 50% of time, limited active play with assistance / supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play; fully able to engage in quiet play
40	Disabled, requires special care and assistance	**40**	Able to initiate quiet activities
30	Severely disabled; hospitalization is indicated though death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick; hospitalization is necessary	**20**	Limited to very passive activity initiated by others e.g. TV
10	Moribund; fatal process progressing rapidly	**10**	Completely disabled, not even passive play
		0	Unresponsive, coma

† **Karnofsky = D.A., et al., Cancer 1: 634-656, 1948**
# **Lansky Scale = Lansky, et. al., Cancer Oct 1; 60(7): 1651-1656, 1987**

10.2 Appendix 2A: Required Study Evaluations

Observation	Eligibility	Pretreatment	On Therapy After 1st & 2nd cycle	On Therapy 3rd cycle	On Therapy 4th & 5th cycle	Off Protocol Therapy 6th cycle	Post Therapy 3 months	Post Therapy 6 months	Post Therapy 18 months
Concurrent meds & PE [1]	X	X	X	X	X	X		X	X
cGVHD Evaluation[2]		X		X		X		X	X
Performance status	X	X		X		X		X	X
Vital Signs with O2 sat.	X	X	X	X		X		X	X
CBC, platelets, differential	X	X		X		X		X	X
Chem 20 panel	X	X	X	X	X	X		X	X
Female urine pregnancy test	X								
BAL Fluid		(X)							
Research Labs with lymphocyte subset panel (Lymphocyte TBNK)		X		X		X		X	X
CMV PCR, blood cultures, urine culture, urinalysis	X								
, HIV1/2 Antibody*, HCV PCR \		X							
Immunoglobulin levels		X				X			
Anti-topoisomerase Ab*		X							
CT Scan of chest		X				X		(X)	(X)
Lung Tissue Specimens		(X)							
Pulmonary Function Tests	X	X	X	X		X		X	X
QOL assessment[3]		X				X	X	X	X
ECG and ECHO* or MUGA*	X								
24 hour urine collection		X		X		X		X	X
2 and 6 minute walk time		X		X		X		X	X
Review of Patient Diaries[t]:			X	X	X	X			

[t] Review of patient diaries to include compliance and toxicity monitoring; this may also be done by phone documentation or documentation during follow-up visit.. [1] Physical examination must be performed every cycle for the first 6 cycles of therapy. This may be included in the cGVHD evaluation for cycles 1-3, 6. [2] Appendix 4 and 6 must be completed. [3] QOL assessments include: FACIT-G, FACT-BMT, HAP, SF-36, and Lee Symptom Score (adults), and ASK and Varni (children). *HIV and HCV antibody, anti-topoisomserase, and ECHO, to be done at NIH only; CMV will be performed at NIH for FHCRC patients. [5]CT scans will be performed at the time points in parentheses at patients treated at NIH, and at FHCRC only if clinically indicated.

10.3 APPENDIX 2B

Study	Responsible Investigator	Time points	Volume	Notes
Leukotriene Assay on Blood	Kirsten Williams, MD Fran Hakim, PhD Ronald Gress, MD 240-760-6167	Baseline, 3, 6 cycles	One-7ml EDTA tube (purple top tube), yielding 3 mL plasma.	All blood/plasma samples to be received and processed by Fran Hakim in the Pre-clinical Services Lab, Building 10 room 12C216. *Total blood samples to be collected include 1 purple top tubes, 1 3ml EDTA, 5-6 CPT tubes for all studies at the 3 time points.
Leukotriene Assay on Urine	Kirsten Williams, MD Fran Hakim, PhD Ronald Gress, MD 240-760-6167	Baseline, 3, 6 cycles	50 mL urine in 2x 25 mL aliquots.	Two 25 mL aliquots of 24 hour urine collection to be sent frozen from Hakim laboratory to Milton S. Hershey Medical Center College of Medicine (MSHCC).
Leukotriene Receptor Expression on Immune Cells by Flow Cytometry and Cytokine Studies	Kirsten Williams, MD Fran Hakim, PhD Ronald Gress, MD 240-760-6167	Baseline, 3, 6 cycles	*5-6 CPT TubesOne-3 mL plasma	Plasma and cells will be processed by the Hakim laboratory in Pre-Clinical Service Lab for batched analysis. One sample will be run fresh, the remainder frozen for subsequent analysis with TBNK.
BAL fluid analysis for Leukotriene Receptor Expression on Immune Cells by Flow Cytometry and Immunohisotochemistry Tissue analysis.	Kirsten Williams, MD Fran Hakim, PhD Ronald Gress, MD 240-760-6167	At time of BAL (adult patients) and any lung biopsy specimens.	~ 500 mL BAL fluid 3 mL frozen for leukotriene analysis at MSHCC. Tissue sections in paraffin	BAL samples will be collected and divided at time of BAL. If adequate volume obtained, BAL fluid will be sent to Pre-Clinical Service Lab for cell processing for flow cytometry studies and 3 mL sent to MSHCC. Tissue sections will be sent to the Gress Lab Building 10 3-3288 for immunohistochemistry analysis.

*Research blood sample aliquot size will be minimized for patients < 10 years of age or < 30 kg and the total amount restricted to a maximum of 3 ml/kg per draw and 7 ml/kg per 6-week period. Patients > age 10 and > 30 kg will have no more than 120 ml blood drawn per 6-week period for research studies. In the event that blood draws are limited due to these restrictions, research studies will be performed in order of priority as listed above. For processing, please see appendix 14.

10.4 Appendix 3: Initial History Guidelines

1. Patient Demographic: **age** (current, at transplant, and at diagnosis of BO), **gender**, ethnicity, **CMV** status, **number** of transplants, history of **asthma**, history of smoking.

2. Donor Demographic: **age**, **relationship, gender,** degree of HLA match at A, B, C, DR, DQ, DP loci and type of match (allele or serologic), **CMV** status, history of **asthma if available. For unrelated donors, this information may not be available**.

3. Underlying Disease Characteristics: **diagnosis**, **stage** at transplant (complete response, minimal disease, recurrent or persistent disease) and **risk** group at transplant, and stage at this presentation, and whether prior therapy included: radiation, bleomycin, busulfan, carmustine, chlorambucil, cyclophosphamide, cytosine arabinoside, docetaxel, etoposide, fludarabine, gemcitabine, methotrexate, mitomycin, paclitaxel, procarbazine, vinca alkaloids.

4. Stem Cell Characteristics: Marrow, peripheral blood, cord blood, CD34 cell dose

5. Conditioning Regimen characteristics: **Myeloablative or non-myeloablative, or reduced-intensity conditioning,** and Regimen used.

6. GVHD **prophylaxis**: cyclosporine, tacrolimus, methotrexate, or other drugs, anti-thymocyte globulin, campath or other T cell targeted antibody therapies, T cell depleted graft or T replete.

7. Early Post-Transplant Events: **acute GVHD and grade** (I-IV), organs involved and stage 1-4, whether or not the patient was steroid refractory, was the patient off all medications for acute GVHD for > 2 months prior to onset of cGVHD? Were **pulmonary infections** present or systemic viral infections, CMV disease/evidence of reactivation in the first 90 days post-BMT? Were **donor lymphocyte infusions** given? (If yes, how many?)

8. CGVHD Treatment history: **date of cGVHD** diagnosis, biopsy proven or clinically diagnosed, and which organs involved, extensive or limited at onset, initial therapy, progressive-de novo-quiescent, subsequent therapies and approximate dates started, whether or not the patient was ever able to discontinue immunosuppression for at least 3 months and approximate date.

9. cGVHD Characteristics at enrollment: **C**urrent cGVHD systemic and local therapies, organs involved, severity: mild vs. moderate vs. severe, limited vs. extensive, or autoimmune phenomena suspicious for cGVHD such as myositis, myasthenia, polyneuropathy, serositis (pleural, pericardial, ascites.

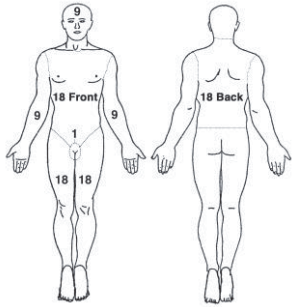
10. Underlying disease characteristics at the time of enrollment
    Underlying disease or second malignancy present at the time of cGVHD diagnosis, stage, and how diagnosed. Current disease status.

11. Bronchiolitis Obliterans History
    Time post-transplant of **diagnosis of BO**, how diagnosis was made (e.g. PFT, biopsy, BAL (negative for infection), CT scan airtrapping). Current symptoms/restrictions. Prior therapies for BO: name, frequency, length of course, complications, time initiated post-transplant, response. All prior PFTs including the pre-transplant PFT (if available) will be requested at the start of the study.

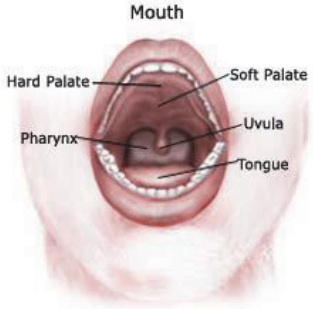
10.5 Appendix 4: Chronic GVHD Activity Assessment- Clinician

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

CHRONIC GVHD ACTIVITY ASSESSMENT- CLINICIAN

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 largest dimension in cm and mark location of ulcer	Location: _____ Largest 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	Moderat (≥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
Icers	None	0	Nne	0	Ulcers involving (≤20%)	3	Severe ulceratios (>20)	6
Mu oœles *	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 ucosal 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 • Nausea & Vomiting	*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* *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 chronic GvHD is mild, moderate or severe?** 0=none 1= mild 2=moderate 3=severe	**Where would you rate the severity of this patient's chronic GvHD 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** **Most severe cGvHD symptoms possible**	**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=A little worse -2=Moderately worse -3=Very much worse

Functional Performance (in persons >4 years old) • Walk Time • Grip Strength	Total Distance Walked in 2 Minutes: Number of laps: _____ (x 50 feet) + final partial lap: _____ feet = _____ feet walked in 2 minutes	Grip Strength (Dominant Hand) Trial #1 psi	Trial #2 psi	Trial #3 psi	Range of Motion: ○ Not performed ○ Physical Therapy Report Attached

Score	Lansky Performance Status Scale Definitions (circle from 0-100) (persons < 16 years old)	Karnofsky Performance Status Scale Definitions (circle from 0-100) (persons 16 years or older)
100	Fully active, normal	Normal no complaints; no evidence of disease
90	Minor restrictions in physically strenuous activity	Able to carry on normal activity; minor signs or symptoms of disease
80	Active, but tires more quickly	Normal activity with effort; some signs or symptoms of disease
70	Both greater restriction of and less time spent in play activity	Cares for self; unable to carry on normal activity or to do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requires occasional assistance but is able to care for most personal needs
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance
30	In bed; needs assistance even for quiet play	Severely disabled; hospital admission is indicated although death not imminent

20	Often sleeping; play entirely limited to very passive activities	Very sick; hospital admission necessary; active supportive treatment necessary
10	No play; does not get out of bed	Moribund; fatal processes progressing rapidly
0	Unresponsive	Dead

10.6 Appendix 5A: Sign and symptoms of cGVHD

ORGAN OR SITE	***DIAGNOSTIC*** *(Sufficient to establish the diagnosis of chronic GVHD)*	DISTINCTIVE *(Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)*	OTHER FEATURES*	***COMMON*** *(Seen with both acute and chronic GVHD)*
Skin	• Poikiloderma • 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** (usually symmetric, affects most nails)		
Scalp and Body Hair		• New onset of scarring or non-scarring scalp alopecia, (after recovery from chemoradiotherapy) • Scaling, papulosquamous lesions	• Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes), • Premature gray hair	
Mouth	• Lichen-type features • Hyperkeratotic plaques • Restriction of mouth opening from sclerosis	• Xerostomia • Mucocele • Mucosal Atrophy • Pseudomembranes** • Ulcers**		• Gingivitis • Mucositis • Erythema • Pain
Eyes		• New onset dry, gritty, or painful eyes† • Cicatricial conjunctivitis • Keratoconjunctivitis sicca† • Confluent areas of punctate keratopathy	• Photophobia • Periorbital hyperpigmentation • Blepharitis (erythema of the eye lids with edema)	
Genitalia	• Lichen planus-like features • Vaginal scarring or stenosis	• Erosions** • Fissures** • Ulcers**		

GI Tract	• Esophageal web • Strictures or stenosis in the upper to mid third of the esophagus**		• Exocrine pancreatic insufficiency	• Anorexia • Nausea • Vomiting • Diarrhea • Weight loss • Failure to thrive (infants and children
Liver				• Total bilirubin, alkaline phosphatase > 2 x upper limit of normal† • ALT or AST > 2x upper limit of normal†
Lung	• Bronchiolitis obliterans diagnosed with lung biopsy	• Bronchiolitis obliterans diagnosed with PFTs and radiology†		• BOOP
Muscles, Fascia, Joints	• Fasciitis • Joint stiffness or contractures secondary to sclerosis	• Myositis or polymyositis †	• Edema • Muscle cramps • Arthralgia or arthritis	
Hematopoietic and Immune			• Thrombocytopenia • Eosinophilia • Lymphopenia • Hypo- or hyper-gammaglobulinemia • Autoantibodies (AIHA, ITP)	
Other			• Pericardial or pleural effusions • Ascites • Peripheral neuropathy • Nephrotic syndrome • Myasthenia gravis • Cardiac conduction abnormality or cardiomyopathy	

*Can be acknowledged as part of the chronic GVHD symptomatology if diagnosis is confirmed
**In all cases, infection, drug effect, malignancy or other causes must be excluded.

†Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer's test foreyes). GVHD (graft versus host disease); ALT (alanine aminotransferase); AST (aspartate aminotransferase); BOOP (bronchiolitis obliterans organizing pneumonia); PFTs (pulmonary function tests); AIHA (autoimmune hemolytic anemia)

10.7 Appendix 5B: Core set of measures for assessing responses in chronic GVHD trials

Measure	Clinician Assessed	Patient Reported
I. Chronic GVHD specific measures		
Signs	Organ specific measures	N/A
Symptoms	Clinician assessed symptoms	Patient reported symptoms Lee Symptom Scale
Global rating	Mild-moderate-severe 0-10 severity scale 7 point change scale	Mild-moderate-severe 0-10 severity scale 7 point change scale
II. Ancillary measures (chronic GVHD non-specific)		
Function	Grip Strength[54-56] 2 min walk time[58]	HAP[57] SF-36v.2[59-61] ASK in children[37, 61, 62]
Performance status	Karnofsky or Lansky[63]	
Quality of life		FACT-BMT[35] in adults VARNI in children[36]

10.8 Appendix 6: cGVHD score sheet

	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 "hideboud" (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
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

	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* **FEV1** ☐	☐ 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)
DLCO ☐	☐ 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
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:** _____

10.9 Appendix 7: Chronic GVHD Manifestations

Component	Items assessed	Measure	Assessor*
Skin	Erythematous and/or papular rash of any sort	% body surface area	C
	Superficial sclerosis (movable)	("rules of 9's)	C
	Deep sclerosis (non-moveable)		C
	Ulcers Largest dimension (cm)	of the largest ulcer	
	Pruritus or itching	0 – 10 scale	P
Eyes	Bilateral Schirmer's tear test scores without anesthesia	Mean of both eyes (mm)	C
	Chief ocular complaint at the time of the visit	0 – 10 scale	P
Mouth	Erythema	Total score 0 – 15	C
	Lichen-type Hyperkeratosis		C
	Ulcerations		C
	Mucoceles		C
	Symptoms of oral pain, dryness, sensitivity	0 – 10 scale	P
Hematology	Platelet count, eosinophils	number/μL	C
Gastrointestinal	Upper GI symptoms	0 – 3 score	C/P
	Esophageal symptoms	0 – 3 «	C/P
	Diarrhea	0 – 2 «	C/P
Liver	total serum bilirubin	mg/dL	C
	ALT, alkaline phosphatase	U/L	C
Lungs	Bronchiolitis obliterans syndrome	FEV1, DLCO	C
Chronic GVHD Symptom scale[34]	30 items, 7 subscales, 1 summary scale	1-100	P
Global activity rating	Severity of chronic GVHD symptoms	0 – 10	C/P
	Perception of change	+3 to -3	C/P
	Overall severity of chronic GVHD	Mild – Moderate-Severe	C/P

- Vulvar-vaginal symptoms (yes or no) and patient weight should be recorded at each visit. Range of motion of the most affected joints should be recorded, depending on the availability of a physical therapist.
*C=assessed by the clinician; P=reported by the patient

10.10 Appendix 8: Lung Function Score

The Lung function score (LFS) is computed by the extent of FEV_1 and DLCO compromise (>80% = 1, 70 – 79% = 2, 60 – 69% = 3, 50 – 59% = 4, 40 – 49% = 5, <40% = 6). The scores for FEV_1 and DLCO are then added together, and the sum is reduced to an overall category according to the following table.

Category	10.10.1 Lung function	10.10.2 LF score
I	Normal	2
II	Mild decrease	3 – 5
III	Moderate decrease	6 – 9
IV	Severe decrease	10 – 12

It is important to emphasize that LFS has never been used in chronic GVHD response assessments and its exact role in this setting needs to be determined. To allow validation in trials absolute values of both FEV_1 and DLCO are recorded on the data collection forms.

10.11 Appendix 9: Physiatry Evaluation:

Walk Test, Grip Strength, Function Scales

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.

The HAP has a standard scoring mechanism which determines normal activity. However, it has not been looked at with respect to disability. We have done this internally for several studies based of internal agreement. The maximum activity score (based on 94 questions) was divided into performance groups: top quartile are normal performers with scores of >81; next quartile with scores of 73-81; next quartile 61-72 and bottom quartile 60 and below.

Human Activity Profile (HAP):

The HAP is comprised of 94 self-report items, each of which represents an activity requiring a known amount of average energy expenditure (metabolic equivalent - MET). The patient answers each item with one of three possible responses: *still doing this activity; have stopped doing this activity;* or *never did this activity.* The HAP yields a variety of scores. The Maximum Activity Score (MAS) is the highest oxygen demanding activity still performed and is determined in comparison with peers of same age and gender. The Adjusted Activity Score (AAS) is the MAS minus the total number of *stopped doing* responses below MAS and represents the average level of activity. The Activity Age represents the age at which 50% of healthy adults of a given age and sex surpass a given MAS. The HAP is designed for ages 20 - 79 with a minimum reading ability of 4th grade. It has been successfully tested for reliability and validity and has age and gender specific norms.

10.12 Appendix 10: Chronic GVHD patient symptom scale

APPENDIX

Please let us know whether you have been bothered by any of the following problems in the past month.

	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:					
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

From Lee et al. BBMT, 8:444-452, 2002 [34]

HCP

Evaluating:_____/Date:_____

10.13 Appendix 11: Patient Diary for Montelukast (Singulair)

Patient ID number:_____**Dose**:_____**Cycle Number (1-6)**:_____**Cycle Start Date**:_____

Date →	Start:							Completion:																					
Day:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Check if Missed Dose→																														
Indicate reason for missed doses →																														

SIDE EFFECTS	**Severity (Mild, Moderate, Severe)**	**Start Date**	**Frequency (e.g. 12 hr)**	**Stop Date**	**Describe Reaction**
OTHER DRUGS (Name)	**Dose**	**Start Date**	**Frequency**	**Stop Date**	**Reason for Use of Medication**

* If you miss a dose write "X" in the box.

Parent/patient signature:_____

Physicians should fax completed form to the NCI Research Nurse each month 301-480-3201, or or brought to follow-up visits.
Please call with questions: 301-451-6569.

10.14 Appendix 12: Chronic GVHD Activity Assessment- Patient Self Report

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

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?	o Yes o No o 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

10.15 Appendix 13: QOL and Functional assessment scales

Scale

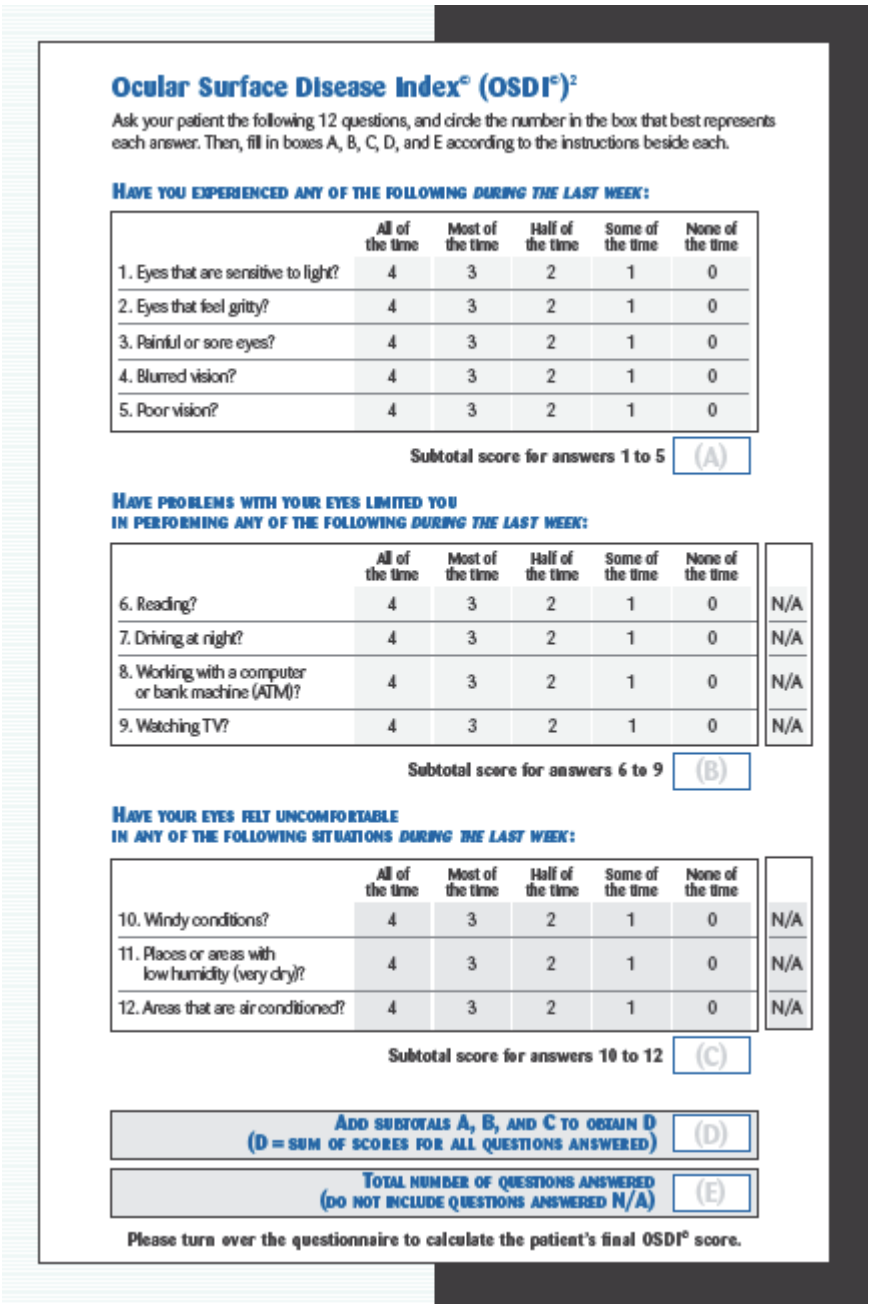
Lee Symptom Scale (please see Appendix 11):
This is a one-page checklist that evaluates patient's symptom bother for 7 different major categories.

Ocular Surface Disease Index (OSDI):
This is a one page questionnaire that evaluates patients ocular symptoms of dry eyes.

Quality of life:
FACT-BMT and FACT-G (adults)
The FACT-BMT and FACT-G are questionnaires that permit patients to score symptoms and other elements that influence well-being in terms of how much these elements interfere with quality of life. The questionnaire addresses physical well-being, social/family well-being, relationship with doctor, emotional well-being, and functional well-being.

VARNI (pediatric)[36]
The VARNI is a pediatric questionnaire that permits pediatric patients to score symptoms and other elements that influence quality of life in terms of how much these elements interfere with childhood day to day activities and quality of life. This test bears a copyright. We have procured the rights to administer this test to all pediatric subjects at all institutions on this trial (only).

Functional Assessment:
The SF-36v.2 (adults) and ASK (pediatric) are questionnaires that capture the functional/physical abilities of the patient by asking a series of questions that indicate whether the patient can perform the task described (e.g. brushing ones own teeth).



Ocular Surface Disease Index© (OSDI©)[2]

Ask your patient the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

ADD SUBTOTALS A, B, AND C TO OBTAIN D (D = SUM OF SCORES FOR ALL QUESTIONS ANSWERED) (D)

TOTAL NUMBER OF QUESTIONS ANSWERED (DO NOT INCLUDE QUESTIONS ANSWERED N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

10.16 Appendix 14: ETIB Policy for Sample Handling

Experimental Transplantation and Immunology Branch
Preclinical Service Policy for Sample Handling

Sample Processing

Bronchial Lavage Fluid (BAL):
Collected at pretreatment timepoint only, from adult patients only.
Expect 35 – 50 ml of fluid.
Filter BAL through 40µm nylon cell strainer (BD Falcon, #352340).
Spin down cells (1500 rpm, 10 min, 10°C) and collect supernatant.
Freeze all of the supernatant in a series of 15ml conical tubes. Label and store at -80°C.
Resuspend BAL cell pellet in 1 ml DPBS. Count. Expect 5 – 10 x 10^6 cells.

At NIH: BAL is being immediately processed for flow cytometry:
If BAL has a significant RBC content, ACK lyse before staining. (Combine 1 ml of BAL cells resuspended in DPBS with 10 ml of ACK, mix well, hold for 5 min at RT, spin down (1500 rpm, 10 min, 10°C), wash in 10 ml FACS buffer, spin down and resuspend in 0.5ml FACS buffer. Add human aggregated IgG and normal mouse serum to block Fc receptors on alveolar macrophages. Distribute to staining tubes.
For NON-NIH Institutions: BAL is being crypreserved:
RBC are not a problem and do not need to be lysed. Do not ficoll.
Follow standard cell freezing protocol.

EDTA plasma:
Spin down cells at 1500 rpm, 10 min, 10°C. Draw off plasma. Store 3 ml of plasma in each of two 15ml conical tubes (total stored plasma = 6ml), labeled as EDTA plasma. Store at -80°C.

Urine:
24 hr urine collections are made at pretreatment, 3 months and 6 months, for analysis of leukotriene content.
Store two 50ml centrifuge tubes from each collection. Freeze at 80°C immediately upon arrival of sample.

Heparinized Blood:
Heparinized whole blood is collected at pretreatment, 3 months and 6 months, for analysis of relevant cytokine/chemokines content. Separate plasma by centrifugation and freeze two 3ml samples in 15ml conical tubes, labeled as heparinized plasma. Store at –80°C.
If whole blood is being processed for flow cytometry:
Place 1 ml of well mixed whole blood in a 15ml tube. Add 10ml ACK. Mix well by repeatedly inverting tube. Hold 5 min RT. Spin down (1500 rpm, 10 min, 10°C), Resuspend in 0.5ml FACS buffer. Distribute to staining tubes.
If whole blood is cryopreserved
Ficoll blood and cryopreserve cells, divided into two 1ml aliquots. Store in LN2.

Our freezing protocol is attached, but any commercial cryopreserve media will suffice.

Labeling. All samples are to be labeled with an anonymized Patient identifier such as the patient # in the B.O. series of patients), date, content (EDTA or heparinized plasma, urine, BAL fluid, PBMC with cell number, BAL cells with cell number) and preferably stage (pre, 3m, 6m). We need to be able to link all timepoints collected on a single patient.

ETIB Preclinical Service
Form for Sending Samples on this protocol

For patients enrolled at Hackensack, we anticipate that the patients will come to NIH for evaluation (including bronchoalvolar lavage and all blood draws) and thus, their samples will be collected in the same manner as the NIH patient samples and sent directly to the Clinical Core Facility as per Appendix 2B. For other IRB-approved institutions on this protocol that have the ability to process samples (e.g. FHCRC), please use the guidelines listed here.

At these institutions, bronchoalveolar lavage fluid, blood, and urine may be obtained as described in this protocol at the following time points: baseline, 3 cycles, 6 cycles, 6 and 18 months post protocol therapy (with the exception of bronchoalveolar lavage fluid that is obtained only once). For bronchoalveolar lavage, the tube will spun down, the fluid frozen as described for urine below, the cells should be resuspended in saline and sent fresh.

For blood specimens, these should be labeled with the date and the patients assigned number on this protocol. Blood specimens should be drawn in the tubes listed. At least 3 ml will be sent in a heparinized tube fresh. The remainder will be handled in Appendix 2B, ficolled, and the white blood cells and plasma stored in a -80 freezer until a batch shipment is readied. This will only performed by experienced technicians through arrangements previously established with the institution after IRB approval at that institution. For questions regarding the handling of samples, please contact: Dr. Fran Hakim at 301 402 3627.

Urine and bronchoalveolar lavage specimens should be similarly handled with labels to include patient number on this protocol and date. Experienced technicians handling these samples at IRB-approved outside institutions should reference 3.4.4.4 and Appendix 2B for sample handling.

When batch shipments are ready, each shipment should be sent to:

Dr. Fran Hakim
12C216 Building 10, 10 Center Drive
Bethesda Maryland 20892

Each sample should be accompanied by the following data: the protocol number, patient's assigned number (on this protocol), the date obtained, the sample type, the date sent, and an accompanying cbc/diff from the same date obtained. Additionally, the technician involved in the

sample preparation and the mailing of samples should both be recorded. Please refrain from including patient identifiers in samples to be shipped to the NIH.

Outside institutions (such as FHCRC) will not be responsible for sending material for leukotriene assays or for any additional requests beyond basic sample processing and shipping to Dr. Hakim at the Clinical Core Facility at NCI. Dr. Hakim will be responsible for sending the samples in batch to the Core Endocrine Laboratory for leukotriene testing and also for biologic studies of patient leukocytes.

Storage/Tracking

Normal donor and patient blood and tissue samples, collected for the purpose of research under IRB approved protocols of the Experimental Transplantation and Immunology Branch, may be archived by the ETIB Preclinical Service. All data associated with archived clinical research samples is entered into the ETIB Preclinical Services'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/post transplant time point, cell source (e. g. peripheral blood, lymphapheresis, mobilized peripheral blood stem cells, marrow, pleural fluid) 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. As of January 2007, all newly received samples will receive a unique bar code number, which will be added to the sample Preclinical Service 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. All non-coded samples previously archived will be stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.

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) (-85° freezer) or in ETIB common equipment space (CRC/3-3273). 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 (appended) 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 (attached) 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.

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 (see attached authorization form from the NCI IRB).

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 (ex. 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.

10.17 Appendix 15: NIH Problem Report Form

NIH PROBLEM REPORT FORM

Use this form to report problems to the IRB that may be:

A. Unanticipated Problems (UPs) including Unanticipated Adverse Device Effects (UADEs)
B. Protocol Deviations (PDs) or
C. Non-compliance

For more information on UPs and PDs, "Principal Investigator (PI) and IRB Reporting Requirements for Unanticipated Problems and Protocol Deviations". For more information on Non-compliance, "Allegations and Incidents of Non-compliance with the Requirements of the NIH Human Research Protection Program (HRPP)."

DEFINITIONS

Protocol Deviation (PD): Any change, divergence, or departure from the IRB-approved research protocol.

The impact of a PD is characterized by designation as serious or not serious PDs include three types of protocol deviations:

A. Those that occur because a member of the research team deviates from the protocol;

B. Those that are identified before they occur, but cannot be prevented (e.g., when a subject alerts the research team that inclement weather will prevent the subject from attending a scheduled protocol visit); and

C. Those that are discovered after they occur.

Unanticipated Problem (UP): Is any incident, experience, or outcome that meets **all** of the following criteria:

A. **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

B. **Related or possibly related** to participation in the research (**possibly related** means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

C. Suggests that the research places subjects or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human research subjects; ("Allegations and Incidents of Non-compliance with the Requirements of the NIH Human Research Protection Program (HRPP).")

Minor non-compliance: Non-compliance that, is neither serious nor continuing.

Serious: A UP or PD 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**.**

*** Serious Adverse Event (SAE):** is any Adverse Event that: 1. Results in death; 2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred); 3. Results in inpatient hospitalization or prolongation of existing hospitalization; 4. Results in a persistent or significant disability/incapacity; 5. Results in a congenital anomaly/birth defect; or 6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

INSTRUCTIONS TO PRINCIPAL INVESTIGATORS

A. Use this form to report all problems to the IRB including UPs, PDs, or Non-compliance

B. Use the appropriate electronic IRB system to complete this form (iRIS or PTMS.) If the PI is unable to access the appropriate IRB reporting system, PI may use this NIH Problem Report Form. The PI may elect also to report events (especially if Serious) to the IRB Chair/designee and/or the CD, in person or by phone or e-mail. However, such reporting is in addition to the required reporting using the NIH Problem Report Form.

C. Any modifications to the protocol and/or consent(s) resulting from a UP, PD or Non-compliance must be submitted via a separate amendment in the appropriate IRB system (iRIS or PTMS), except when necessary to eliminate apparent immediate hazard to the subjects– "Amendments to IRB-approved Research".

D. Additional reporting requirements may apply, e.g., to the FDA, the NIH Office of Biotechnology Activities (OBA).

IMPORTANT: Notify the IRB and Clinical Director using the following timeframes:

A. **Serious UPs, UADEs, Serious PDs, and Serious Non-compliance:** as soon as possible, but not more than seven (7) days after the PI first learns of the event.

B. **Not Serious UP, Not Serious PD or Minor Non-compliance:** not more than fourteen (14) days after the PI first learns of the event.

NIH PROBLEM REPORT FORM

NCI Protocol #:	**Protocol Title:**
	Report version: *(select one)* ____Initial Report ____Revised Report ____Follow-up
Site Principal Investigator:	
Date of problem:	**Location of problem:** *(e.g., patient's home, doctor's office)*
Who identified the problem? *(provide role (not name of person): nurse, investigator, monitor, etc…)*	
Brief Description of Subject *(if applicable)* (*Do NOT include personal identifiers)*	Sex: ___ Male ___ Female Age: ___ Not applicable (more than subject is involved)
Diagnosis under study:	

Name the problem: *(select all that apply)*

[ ] Adverse drug reaction
[ ] Abnormal lab value
[ ] Death
[ ] Cardiac Arrest/ code
[ ] Anaphylaxis
[ ] Sepsis/Infection
[ ] Blood product reaction
[ ] Unanticipated surgery/procedure
[ ] Change in status (e.g. increased level of care required)
[ ] Allergy (non-medication)
[ ] Fall
[ ] Injury/Accident (not fall)
[ ] Specimen collection issue
[ ] Informed consent issue
[ ] Ineligible for enrollment
[ ] Breach of PII
[ ] Tests/procedures not performed on schedule
[ ] Other, brief 1-2 word description: _____

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*):

***Is this problem unexpected?** *(see the definition of unexpected in the protocol))* __YES __NO **Please explain:**
***Is this problem related or possibly related to participation in the research?** __YES __NO **Please explain:**
***Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized?** __YES __NO **Please explain:**
Is this problem? (*select all that apply*) [ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious [ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance **Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] AE [ ] Non-AE
Have similar problems occurred on this protocol at your site? __YES __NO **If "Yes", how many? ____ Please describe:**
Describe what steps you have already taken as a result of this problem:
In addition to the NCI IRB, this problem is also being reported to: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**

INSTITUTE: National Cancer Institute

STUDY NUMBER: 08-C-0097 PRINCIPAL INVESTIGATOR: Ronald Gress, M.D.

STUDY TITLE: Multi-Institutional Prospective Phase II Study of Montelukast for the Treatment of Bronchiolitis Obliterans Following Allogeneic or Autologous Stem Cell Transplantation in Children and Adults

Continuing Review Approved by the IRB on 03/21/16
Amendment Approved by the IRB on 01/18/17 (N) Date Posted to Web: 01/27/17

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.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

Recently, you had a bone marrow or stem cell transplant (BMT/SCT) to help treat a disease, and as a side effect of that transplant, you were diagnosed with Bronchiolitis obliterans (also called BO). This is a form of chronic graft versus host disease (cGVHD) that sometimes occurs after blood and marrow or stem cell transplant (BMT/SCT). This is why we are inviting you to participate in this research study. In BO, white blood cells (that normally fight infections) attack

the lungs of the recipient of the transplant. This attack of white blood cells leads to destruction of lung tissue and scarring. The scarring is called fibrosis. When a patient develops fibrosis of the lungs, the lungs can no longer work properly. Thus, the patient may develop difficulties with breathing, becoming short of breath with minimal exercise. In severe cases, some patients may require oxygen to help them breathe. This leads to a diminished quality of life and an increased risk of death.

This is a trial of montelukast (or singulair) for children and adults with BO after BMT/SCT. Montelukast is a drug that has been used for many years to treat asthma, another lung condition. This drug has been approved by the U.S. Food and Drug Administration (FDA) to treat asthma, but has not been approved to treat BO, therefore, its use in this research study will be considered experimental. In a published study, this drug has recently been proven safe to treat other forms of chronic graft-versus-host disease (cGVHD) after BMT/SCT. There have also been promising studies using montelukast in other diseases where the new immune cells attack the recipient tissues or organs. This drug has been widely used in children and adults and has been deemed very safe. Montelukast is a drug that decreases inflammation and scarring of lung tissue.

Purpose of the Study:

The purpose of this study is: 1) to see if montelukast improves or stabilizes your lung function, since you have BO after BMT/SCT, 2) to assess the safety of montelukast in patients with BO after BMT/SCT, 3) to test if montelukast affects the cells that hurt the lungs by testing the blood or urine of patients with BO after BMT/SCT, and 4) to see if montelukast improves other forms of cGVHD, quality of life, and overall survival in patients with BO after BMT/SCT.

Study Design:

Approximately 45 people with BO will be treated on this trial. This study will enroll adults and children over 6 years old. In this trial, you will receive montelukast at an FDA-approved dose for your age. Montelukast is an oral medication; you will take 1 tablet once daily, each night, for 6 months. This medication may be taken with or without food. (For patients unable to swallow pills, the tablets will be chewable). During the 6 months you are taking montelukast as part of this research study, you will be asked to complete a medication diary to record when you took the medication, any other medications you were taking, and any side effects you experienced during that time. If, at the conclusion of the first six months, you and your doctor would like you to continue this medication, you will be able to do so within the context of this study as long as you tell the trial coordinators you would like to do so. You will be able to continue on your other medications (if applicable) for cGVHD after you start this research study.

You will need to be monitored while taking montelukast on this trial. Once a month for the first three months, you will have pulmonary function tests (PFT) performed to monitor your lung function. To do a pulmonary function test, you will be asked to breathe into a machine to follow

your lung function. This test will measure the amount of air that goes into and out of your lungs as you breathe. This test will also need to be done at 6 months, 12 months, and 24 months after starting the study medication.

You will have a complete medical history and physical examination done approximately every 3 months for the first year of the study and then at 12 months and 24 months after starting the study medication at any site where this trial is open. You will need to have a physical examination done monthly for the first 6 months of the trial, at your primary doctor's office.

We will be following you on this research study for up to 24 months after starting the study medication. This study is designed to last six months, with a possible continuation for up to 24 months. The NCI will supply the study medication (montelukast) for the first six months of the study, but thereafter, you will have to obtain a prescription for montelukast from your primary doctor if you wish to continue with this treatment. The decision about whether or not to continue the study medication beyond six months will be up to you and your doctor. During the study period of 6 to 24 months, you will be primarily seen by your primary care doctor.

Below is a table to help you understand when you will have the study procedures done:

Day	What will be done
Before starting study	• To determine if you are eligible on this study: • Have your medical history collected and a physical examination • Have routine blood work performed to test your liver function • Have your heart and lung function tested • Sign informed consent form to enroll on this study
Baseline (day 1 on study)	• Medical history and physical exam (includes an evaluation of cGVHD) • Labs including an HIV test, urine and blood • Lung function test (also known as a Pulmonary Function Test or PFT) • Chest CT scan • Bronchoalveolar lavage for adult patients • Quality of Life Questionnaires

Day	What will be done
Day 1 – Month 6	• Begin taking montelukast, 1 tablet, once a day. Keep taking montelukast until the end of study, unless told to stop by your health care team. • Write down the dose of montelukast you took each day in your medication diary, along with any side effects you experienced and/or any other drugs you took.
Month 1	• Lung function test (PFT) • Labs (blood)
Month 2	• Lung function test (PFT) • Labs (blood)
Month 3	• Medical history and physical exam (includes an evaluation of cGVHD) • Labs (urine and blood) • Lung function test (PFT)
Month 4, 5	• You will have a visit to your local doctor for a physical examination, and a blood test for your liver function
Month 6	• Medical history and physical exam (includes an evaluation of cGVHD) • Labs (urine and blood) • Lung function test (PFT) • Chest CT scan • Quality of Life Questionnaires
Month 9	• Quality of Life Questionnaires (mailed to you)
Months 12 & 24	• Medical history and physical exam (includes an evaluation of cGVHD) • Labs (urine and blood) • Lung function test • Chest CT scan • Quality of Life Questionnaires

Evaluations:

Prior to starting therapy, we will need to review your medical records and lung evaluations to determine if you have BO after BMT/SCT and to determine if you meet criteria to be enrolled on this study. At a minimum, this study will require the collection of blood specimens and clinical data, which we describe below. The purpose of this baseline (first) visit is to evaluate your eligibility for this trial. Examinations during this trial may include the following:

History and physical Examination: A summary of your medical record will be requested from your physician when you are initially referred to the NIH. During the baseline visit, we will also review your medical history with you and perform a detailed physical examination, including a 2 and 6 minute walking test to test how well you breathe with exercise. If you have had prior biopsies of the lung done, we request permission to have these sent for further evaluation at the NIH, but we do not require a lung biopsy for this study.

Blood Tests: During your baseline visit, blood will be drawn from either a vein in your arm or a central line (if you have this). About 3 tablespoons of blood will be used to measure your blood counts, liver and kidney function, and other routine tests, a test for a virus called cytomegalovirus, and Hepatitis C. After you are enrolled on this study, you will also have an HIV test, the virus that causes AIDS. If you are infected with HIV you may be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report newly diagnosed HIV infection, and the importance of informing your partners at possible risk because of your HIV infection. Also, approximately every 3 months, additional blood will be drawn (approximately 5 tablespoons) for research purposes to study the biology of GVHD and the effects of this new study medication.

Urine Tests: During your visits, we will request urine tests (including a pregnancy test for women at the baseline visit). Additionally, at baseline, 3, and 6 months after starting this study medication, we will test your urine for research purposes to study the biology of GVHD and the effects of this study medication.

Pulmonary Function Test/Lung Function Test: Pulmonary Function Tests or PFTs measure the amount of air that goes into and out of the lungs as a person breathes. BO leads to changes in these amounts that we can follow with this test. You will be asked to breathe into a machine to perform the PFT at the baseline visit, and at various intervals during this study to follow your lung function.

Bronchoalveolar Lavage (BAL): BAL tests are used regularly in the care of patients with lung diseases and GVHD. This procedure has been used safely for many years. An experienced physician performs this test by putting a tube into the airway (bronchoscopy) and putting a small amount of fluid into the lung. This fluid is then removed and can be tested to look for infections or other lung problems. You will be asked not to eat or drink anything six hours prior to the test to minimize the risk of vomiting. Your mouth, nose and airways will be numbed with medication (lidocaine) and the tube (bronchoscope) will pass through your nose into the airway. Some individuals may require sedation or anesthesia for this procedure. Samples of cells and secretions will be obtained by rinsing the airway with sterile salt water. This procedure takes approximately 15-30 minutes. This procedure will be done once as part of this study. You will be asked to sign a separate procedure-specific consent form for this procedure.

If you are an adult (over 18 years old), we will use this test to screen for infection of your lung and to study the biology of GVHD with any extra fluid obtained during this procedure. You will undergo this test once before enrolling on this research study. The BAL test will not be performed on children (less than 18 years old), except if the study doctors are very concerned about an infection in your child, we may ask you to consent to this test for them. In this situation, if there is extra specimen obtained, this could be used for research purposes. If for any reason we feel that this test would be important at a future time, we would consent you separately for this later procedure.

Apheresis: You will be asked to allow us to collect some of your white blood cells. This is optional for the study and would be done by an apheresis procedure, a common method for collecting these cells from the blood. Apheresis is done using a machine that can separate the white blood cells from the rest of the blood. To do this, two intravenous catheters(I.V.s) are usually needed. This means two needle sticks, one in each arm. Your blood is circulated through this machine; the machine separates the white blood cells and collects them. The rest of the blood is returned back to your body with a small amount of salt solution (saline) and blood thinning medication (anticoagulant). Blood thinning medications, such as heparin and/or citrate, are used to keep your blood from clotting during the procedure. The apheresis procedure usually takes approximately 1 hour. The collected cells will be used to study the biology of GVHD and BO.

Chest (CT) Scan: A computerized tomography (or CT) scan uses x-rays to image the body. With this test, multiple small pictures are taken at different levels of the inside of the body. The CT scan may require the injection of dye (contrast) through a needle placed in your arm. CT scans can also be done with oral contrast that you drink. The scan takes between 5 and 10 minutes to complete. During this scan, we may ask you to breathe in a certain way to allow us to

capture an image after you have released the air from your lungs (exhaled). For this research study, you will have this test performed at baseline, 6, 12, and 24 months after starting the study medication.

Echocardiogram: If you have not had a test of your heart function (echocardiogram) within the 3 months prior to starting this research study, you will need to have this test performed. To do this test, a small instrument will use ultrasound waves to look at your heart by placing this instrument on your chest. This test takes approximately 15-30 minutes.

Quality of Life questionnaires: We would like learn how your illness affects your behavior and everyday activities and whether this medication affects these things. You and/or your child will be asked to fill out a couple of questionnaires during this study. These will take about 60 minutes to complete.

RISKS OR DISCOMFORTS OF MEDCATION:

Montelukast (singulair): Montelukast has been used in over 2 million patients to treat asthma (another lung condition). Montelukast has been used in approximately 15 patients with GVHD and approximately 9 patients with BO and GVHD. This drug has few side effects and has been well-tolerated in the patient groups studied.

Side effects:

Likely (occurring in greater than 20% of patients on montelukast drug studies):	**Less likely** (occurring in greater than 2% and less than 20% of patients on montelukast drug studies):	**Rare** (occurring in less than 2% of patients on montelukast drug studies):
• None reported	• headache, • abdominal pain, • heartburn, • cough, • flu, • increased liver function lab test	• fatigue, • fever, • nasal congestion, • dizziness, • abnormal urine test, • agitation including aggressive behavior, • allergic reactions (including swelling of the face, lips, tongue, and/or throat, which may cause trouble breathing or swallowing, hives and itching, and very rarely, chills, low blood pressure, fast heart rate, wheezing, difficulty breathing, and death), • bad/vivid dreams, • increased bleeding tendency, • bruising, • depression, • diarrhea, • drowsiness, • hallucinations (seeing things that are not there), • hepatitis (liver inflammation), • indigestion, • stomach infection,

		• inflammation of the pancreas, • irritability, • anxiousness, • joint pain, • dental pain, • muscle aches and muscle cramps, • nausea, • palpitations, • pins and needles/numbness, • restlessness, • seizures (convulsions or fits), • suicidal thoughts and actions, • swelling, • tremor, • trouble sleeping, and • vomiting.

However, it is possible that this medication will affect you differently and may cause side effects not seen in larger clinical trials for different diseases. You will be closely monitored for side effects to montelukast. If serious side effects develop, the medication amount will be adjusted or discontinued.

Also, you should avoid the following medications during the first six months of this study because these medications can interact with montelukast: rifampin, Phenobarbital or greater than one adult dose per day of aspirin or ibuprofen (e.g. 800 mg for ibuprofen and 650 mg for aspirin) or one pediatric dose per day (less than 10 mg per kg to a maximum of 800 mg ibuprofen; children should not take aspirin due to risk of Reye's syndrome unless specifically prescribed by their physician). We also recommend that rifampin and Phenobarbital never be taken with montelukast because it may be dangerous. However, ibuprofen or aspirin are not harmful if taken with montelukast, but we ask you not to take more than one adult dose of these 2 medications for the first 6 months because they may decrease the benefit of montelukast.

RISKS OR DISCOMFORTS OF PROCEDURES:

Blood Draw: You may experience mild pain or bruising at the site on your arm from which the blood was drawn. There is a small possibility of fainting and infection. Similarly, there is a small risk of bleeding, blockage, or inflammation or infection of the vessel. Discomfort does not usually last long and permanent damage is extremely rare.

Pulmonary Function Test: These tests are very safe and side effects are unlikely. During the test, you will be asked to breathe deeply or rapidly which may occasionally cause brief lightheadedness or soreness of the chest. In extremely rare cases, this may result in the release of a small amount of air from the lung into the lung cavity which would be treated appropriately.

Imaging, Scans and Radiology Tests (CT scan): This research study involves CT scans that do involve minimal exposure to radiation for medical reasons. The most common discomfort is due to the necessity to lie flat during the scanning procedure.

Bronchoalveolar Lavage (BAL):

The potential risks of this procedure are:

- There may be some mild discomfort associated with the procedure because of coughing. This can be controlled by topical medication.
- A decrease in the amount of oxygen in the blood. You will receive additional oxygen during the procedure to help this and you will be closely monitored for oxygen levels, heart rate and blood pressure during the procedure. The risk of a serious problem occurring is very small (less than 1 out of 10,000 procedures in published studies).
- Rarely, a slow or irregular heartbeat occurs. If it does not correct itself, we can treat this with medication. You will be continuously monitored by a heart rhythm monitor (electrocardiograph) during the procedure.
- Mild bleeding from the nose can occur because the bronchoscope tube is placed through the nose to reach the large airways. Placing medication and lubricant inside the nose will be done before the procedure to lower the risk of this occurring.
- Less than 10% of individuals who undergo this kind of procedure develop a sore throat for several hours after the procedure because the broncoscope travels through the back of the throat.

- Rarely, an individual may have a bad reaction to the numbing medication (lidocaine). Side effects can include confusion or, very rarely, seizures. We have never seen this problem in over 1500 bronchoscopies performed in the Medical Intensive Care Unit at NIH over an 8-year period. This potential problem is minimized by using small, frequent doses of the medication.
- A fever has been reported to develop in less than 5% of healthy volunteers six to eight hours after the bronchoscopy.
- The risk of an infection in the lungs due to the procedure is very low. This could result from swallowing saliva from the mouth or from the stomach into the lung airways. To minimize this risk, we ask you to not eat or drink for at least six hours before the bronchoscopy. In addition we give two doses of antibiotics around the time of the bronchoscopy to minimize the potential risks of any secretions carried into the airways by the bronchoscope.
- Individuals with lung disease may be at greater risk of complications from bronchoscopy, although bronchoscopies with bronchoalveolar lavage are performed commonly for such patients without any serious complications or effects.
- There are risks associated with the medicine to make you drowsy to do this procedure. These risks will be explained to you and you will be consented separately at the time of the procedure.

Risks to fetus:

Pregnant and nursing mothers are not able to participate in this research study because of unknown risks to the developing fetus. If you are of child-bearing potential, you must agree to use an effective form of contraception while participating in this research study. Effective forms of contraception include one or more of the following: intrauterine device (IUD), hormonal (birth control pills, injections, or implants), tubal ligation/hysterectomy, partner's vasectomy, barrier methods (condom, diaphragm, or cervical cap), or abstinence.

Risks of research apheresis procedure:

The most common side effects of apheresis are pain and bruising at the IV needle sites. Mild side-effects from the blood thinning medication citrate are common and include chills, numbness and tingling sensations ("pins and needles") especially around the mouth, anxiety, muscle cramps, and nausea. These side effects usually go away quickly when the machine collecting the blood is slowed down. More serious side effects can occur because of low calcium levels due to the citrate used during the procedure. These side effects are uncommon and include low blood pressure, seizures, weakness, and muscle stiffness. If any of these side effects occur, the

apheresis procedure will be stopped, after which these symptoms usually go away. In attempt to decrease the risk of citrate side effects, calcium and magnesium may be given through the IV during apheresis. Risks of this include changes in the heart rate and blood pressure and severe burn injury if calcium leaks out of the IV under the skin. These side effects are unlikely since calcium and magnesium would be given slowly through the large IV used for apheresis. You will be monitored closely for any side effects and the procedure will be stopped and appropriate treatment administered if necessary.

Please circle and initial if you agree or disagree to having a research (optional) apheresis procedure.

I agree_____ I disagree_____

Potential Benefits of Participation:

The potential benefit of this treatment is that it might improve or slow the progression of your BO. Treatment may also improve your other GVHD symptoms. However, this cannot be guaranteed. It is possible that the study medication does not directly benefit you. However, your participation will also help us to learn more about GVHD and this may result in better treatments for your disease in the future.

Alternative Approaches or Treatments:

You may be eligible for other treatments for cGVHD or BO including medicines that slow down the immune system or other investigational treatments. You may elect to receive no further treatment. You may receive the study drug without being on this research study, if your physician agrees to prescribe it. You should discuss these alternatives including their possible risks, benefits, advantages, and disadvantages with your referring doctor and the NIH doctors.

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 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 the study doctor decides to end the study

If this happens, 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 to that point may still be provided to Dr. Gress 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.

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.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. 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), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

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.

Compensation:

There is no compensation for your participation in this study.

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.

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 they 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. I f 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, Dr. Ronald Gress, 10 Center Drive, CRC 3-3330; Telephone: 240-760-6167. If you have questions about optional studies, or would like to withdraw your specimens or data from that portion of the study, please contact the NCI Clinical Director at 240-760-6070.

You may also call the Clinical Center Patient Representative at 301-496-2626

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 MARCH 21, 2016 THROUGH MARCH 20, 2017.

_____ _____ _____ _____
Signature of Investigator Date Signature of Witness Date

_____ _____
Print Name Print Name