Abbreviated Title: Clobetasol rinse for oral cGVHD

NCI Protocol #: 12C0068

Version Date: 3/25/2025

NCT Number: NCT01557517

Title: A Randomized Double-Blind Pilot Study of Topical Clobetasol 0.05% Oral rinse for Oral Chronic Graft-Versus-Host Disease

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Drug Name:	Clobetasol
IND Number:	77313
Sponsor:	Center for Cancer Research
Manufacturer:	Spectrum Chemicals

PRÉCIS

Background:

- Chronic Graft versus Host Disease (cGVHD) is a major late complication of allogeneic hematopoietic stem cell transplantation.
- The oral cavity is the second most commonly affected area in cGVHD and is a major cause of morbidity.
- Clobetasol is a high-potency topical corticosteroid widely used for a variety of inflammatory disorders of the skin and oral mucosa.
- Treatment of oral cGVHD by topical agents is an attractive strategy to potentially avoid adverse effects associated with systemic immunosuppression.

Objective:

- To investigate efficacy of topical clobetasol 0.05% oral rinse for oral chronic graft-versus-host disease (cGVHD)

Eligibility:

- Patients age 12-99 years with clinically significant oral cGVHD.

Design:

- This is a randomized, double blind, placebo-controlled, pilot study of clobetasol 0.05% topical oral rinse with an open label extension period.
- Patients will rinse oral cavity with 10cc of clobetasol 0.05% or placebo oral rinse for 2 minutes 3 times a day.
- Treatment duration will be for 2 weeks in the randomized phase and 2-4 weeks in the open label phase.
- Up to 40 patients will be enrolled on this pilot trial until 34 evaluable patients are assessed.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To investigate efficacy of topical clobetasol 0.05% oral rinse for oral chronic graft-versus-host-disease (cGVHD) during a four-week treatment period as assessed by Oral Mucositis Rating Scale (OMRS).

1.1.2 Secondary Objectives

1.1.2.1 To assess the effect of topical clobetasol on oral cGVHD related pain, sensitivity, and dryness.

1.1.2.2 To evaluate the basic pharmacodynamics and pharmacokinetics of clobetasol mouth rinse in cGVHD patients.

1.1.2.3 To obtain a pilot assessment of patient perceived oral health in cGHVD and its response to treatment with topical clobetasol.

1.1.2.4 To evaluate the validity of the NIH Oral cGVHD Clinical Scoring instrument.

1.1.2.5 To evaluate the immunological profile present at baseline and after clobetasol treatment in oral tissue to identify potential biomarkers for disease response or resistance to clobetasol.

1.1.2.6 To evaluate blood and saliva to identify potential biomarkers for oral cGVHD disease activity and response to topical clobetasol.

1.2 BACKGROUND AND RATIONALE

1.2.1 Chronic Graft-Versus-Host-Disease

Allogeneic hematopoietic stem cell transplantation (alloHSCT) has been used increasingly for malignant and non-malignant disorders [1]. Graft-versus-host disease (GVHD) is a major complication and a leading cause of morbidity and mortality in recipients of alloHSCT. GVHD results from immunologic attack by the donor's immune cells on the recipient's tissues and organs. Incidence and severity of GVHD vary depending on degree of mismatch of major histocompatibility antigens of the donor and host, age of donor and recipient, source of stem cells, and type of preparative regimen[2]. Development of non-myeloablative conditioning regimens has led to a decrease in early post-transplant mortality and an increase in chronic GVHD (cGVHD). Almost 70% of patients who survive more than 100 days after alloHSCT will develop cGVHD, with the majority manifesting in the first year.[2-5] The undersupply of related donors led to expanded use of unrelated and partially matched unrelated donors. Use of non-myeloablative conditioning regimens is related to more frequent use of both older donors and recipients[6]. Taken together, these factors have increased the incidence of cGVHD.

Chronic GVHD has many similar features of autoimmune diseases, such as lupus, lichen planus, and scleroderma, and can have a varied clinical presentation. Mononuclear cellular infiltrates are found in many areas of the graft recipient, including the liver, skin, oral mucosa, and salivary glands[7]. Recent NIH consensus conferences proposed new criteria for staging of cGVHD that consider extent of the disease, number of involved organs, and severity of functional impairment[2,8,9]. Some of these criteria have been validated, and others require validation in future trials[2,4,8,10-12]. Chronic GVHD can persist for months to years and requires long-term multidisciplinary management.

1.2.2 Oral involvement in cGVHD

Oral cGVHD is a common, major cause of morbidity and decrease in health-related quality of life (HRQOL) in long-term alloHSCT survivors[10,13-15]. In a recent randomized trial of peripheral blood stem cell (PBSC) vs. bone marrow stem cells (BMSC) transplants, oral mucosal changes were the most common manifestation of cGVHD in BMSC recipients and the second most common (after skin) in PBSC transplants. Overall incidence in cGVHD was around 85%[3]. Oral manifestations of cGVHD include lichen planus-like changes, mucosal atrophy and ulcerations, taste disturbances, and salivary gland hypofunction. Oral pain and food sensitivity are common, and not limited to patients with ulcerations[10,16,17]. Oral discomfort was shown to be associated with decrease in food intake and weight loss in this group of patients[10,18]. Recently, the contribution of oral cGVHD to inferior health-related QOL was reported [10,19]. There have been several reports of increased incidence of oral squamous cell carcinoma (SCCA) after allo-HSCT, with history of oral cGVHD identified as an independent risk factor[20,21].

1.2.3 cGVHD Therapy

1.2.3.1 Systemic and topical corticosteroids

The treatment for cGVHD consists of various systemic immunosuppressive agents, most commonly systemic corticosteroids, cyclosporine, tacrolimus, mycophenolate, sirolimus and phototherapy[9]. Long-term immunosuppressive treatment for GVHD has a variety of serious complications including life-threatening infections, aseptic bone necrosis, hypertension, and secondary diabetes.[6,22]

Corticosteroids are the most commonly used systemic treatment of both acute and chronic GVHD. Immunosuppressive and anti-inflammatory effects of corticosteroids are mediated through multiple mechanisms including immune cell apoptosis and interference with dendritic cell maturation. The critical role of dendritic cells in the development of GVHD has been outlined in several studies. One study demonstrated the potential of GVHD prevention via depletion of host antigen presenting cells in a murine model.[23]. In another animal study, local depletion of Langerhans cells in skin prevented GVHD. Corticosteroids have been shown to prevent development of dermal dendritic cells *in vitro*.[24]. Additionally, topical corticosteroids induced apoptosis in the murine epidermal Langerhans cells and $CD8^{+}$T cells[25].

Topical corticosteroids such as dexamethasone 0.01% oral rinse and clobetasol 0.05% ointment are used widely for treatment of oral cGVHD, although their efficacy has not been formally evaluated in this condition[4]. Ointments and creams have a disadvantage of uneven and cumbersome application, furthermore, it is difficult to estimate the systemic versus local effect. Unlike solutions used as rinses, ointments can be easily swallowed and absorbed through the gastrointestinal tract. At the NIH Clinical Center, both dexamethasone oral rinse and clobetasol ointment have been used with variable success. In general, complicated application procedures reduce compliance and make evaluation of response difficult. Oral rinses have a particular advantage when a significant oral cavity area is affected as the contact with the entire surface is ensured with potential decrease in systemic absorption.

1.2.3.2 Clobetasol

Clobetasol is a readily available corticosteroid used topically in a wide variety of inflammatory conditions. Clobetasol 0.05% ointment is FDA approved for the treatment of inflammatory skin diseases and clobetasol spray is approved for psoriasis. Clobetasol ointment is widely used topically by oral medicine practitioners for the treatment of oral ulcerative conditions including oral lichen planus, a condition clinically and pathologically similar to oral cGVHD and has been shown to be safe and effective[26-28]. When used 2 times a day for 4-8 weeks, the response rates exceeded 90%.[28,29] There are few side effects associated with oral topical corticosteroid use with the most common being oral candidiasis. To reduce incidence of oral candidiasis infection, patients will be asked to swish and spit once per day with nystatin (100,000u/ml) rinse, which is a standard preventative measure in high-risk patients. Although there have been reports of adrenal suppression associated with high potency topical steroids, these were generally rare and occurred primarily in young children and in patients with large surface areas of involvement (skin). In one study, no changes in morning cortisol levels were observed when clobetasol was applied topically in the oral cavity for 2 months for oral lichen planus.[23] However, other reports have indicated signs and symptoms of adrenal suppression in patients with severe erosion of the oral mucosa, as in erosive oral lichen planus, and long term use (years) of topical clobetasol[30,31]. The effect of clobetasol and other steroids applied topically in the oral cavity on the ability of adrenal glands to respond to stress levels of ACTH has not been formally evaluated in cGVHD or in normal patients.

1.2.4 Trial Plan

Treatment of oral GVHD by topical agents is an appealing strategy because it would potentially avoid the adverse effects associated with systemic immunosuppression and reduce systemic exposure to glucocorticoids. Most importantly, using immunosuppressive agents locally would concentrate the treatment effects for potential maximum benefit. Conversely, use of systemic

agents for the same purpose would interfere not only with the undesirable GVH response, but also with immune responses directed against the malignancy (the graft vs. tumor effect), which is the principal mechanism through which reduced intensity transplants achieve sustained disease remission.

Therefore, we propose this pilot randomized double blind placebo controlled trial of topical clobetasol 0.05% oral rinse for oral cGVHD. Consenting subjects with clinically significant oral cGVHD will be randomized to receive clobetasol or placebo oral rinse for 2 weeks. All subjects will be evaluated biweekly. Clinically significant oral cGVHD is defined as a score of 20 or greater on the Oral Mucositis Rating Scale (OMRS) based on the patient cohort (over 250) seen in the NIH natural history of cGVHD protocol. At the first 2 week appointment, patients will be unblinded and subjects randomized to placebo will be assigned to additional 2-4 week open label treatment period with topical clobetasol rinse. All patients will therefore complete 4 weeks of treatment with the study drug (2 additional weeks for patients originally assigned to clobetasol arm and 4 weeks for patients assigned to placebo arm). All patients will be reevaluated 1 month following the open label period to evaluate the response and collect follow-up data.

Patients with progressive disease while on the clobetasol treatment as determined at any scheduled evaluation visit will be considered non-responders for the primary endpoint evaluation and will be taken off-study. Within 90 days of the end of the open label treatment period, all patients with evidence of benefit (response or stable disease) will be given an option to continue treatment with clobetasol 0.05% with or without additional treatment as deemed clinically necessary, up to one month. The proportion of responders in the active and placebo arm will be used as the primary outcome variable. As no standard definition of oral cGVHD response exists, for purposes of this pilot study, response will be defined as decrease of 25% or more on the OMRS (**Appendix A**). Difference in OMRS scores between the groups at the end of the 2 week blinded period and the change in OMRS score between beginning and the end of the 4 week treatment period with clobetasol oral rinse will serve as a secondary outcome variables. The study schedule of events is outlined in **Appendix E**.

The placebo design is justified by the following: a) there is no proven standard topical therapy for oral cGVHD, b) patients will be unblinded after 2 weeks of treatment (defined in Section **3.2.4**) and those on placebo will be allowed to cross over to the alternate treatment arm. This will allow all participants to receive the study drug for 4 weeks.

In addition to potential direct benefit to the cGVHD patients, this study is likely to provide valuable insights into the cellular and molecular alterations associated with the development of cGVHD and treatment with topical corticosteroids. This will lead to better understanding of the pathogenesis of cGVHD needed as the foundation for development of new therapeutic interventions.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Age: 12 years – 99 years.

2.1.1.2 Diagnosis: clinically significant oral cGVHD after allogeneic HSCT with severity score of at least 2 on erythema subset and/or at least 1 on ulceration subset and a composite

score ≥20 of the Oral Mucositis Rating Scale (OMRS) scale (**Appendix A**) confirmed by the principal investigator (PI), clinical study chair (CSC), or lead associate investigator (LAI).

2.1.1.3 Hematologic Function: Patients must have a platelet count ≥20,000/μL at the time of the initial evaluation.

2.1.1.4 Informed Consent: All patients or their legal representative (for patients <18 years old) must sign an IRB approved informed consent document (cGVHD natural history protocol 04-C-0281 or any NCI protocol allowing for screening procedures) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal representative must sign the protocol specific informed consent. For pediatric patients age appropriate assent will be obtained in accordance with NIH guidelines.

2.1.1.5 Patients must be able to rinse and expectorate study medication rather than swallow it. Female patients must be willing to practice birth control (including abstinence) during and for two months after treatment, if of childbearing potential.

2.1.1.6 Patients must have the ability and willingness to come to Clinical Center for bi-weekly follow-up appointments.

2.1.1.7 No change in systemic immunosuppressive therapy (type or intensity level) within 2 weeks prior to enrollment.

2.1.1.8 A 7-day washout period is required if patients are currently using another oral topical treatment for mouth lesions. Patients currently using clobetasol oral topical treatment are not eligible for this study.

2.1.2 Exclusion Criteria

2.1.2.1 Documented hypersensitivity to clobetasol.

2.1.2.2 Use of clobetasol ointment intra-orally at any time during the last 6 weeks period.

2.1.2.3 Pregnant or breast-feeding females due to possible toxicity to the fetus or infant.

2.1.2.4 Inability to understand the investigational nature of the study to provide informed consent.

2.1.2.5 Patients who, for medical or other reasons, are unable to comply with the study procedures.

2.2 SCREENING EVALUATION

Evaluation outlined in Section **3.3.1** and **Appendix A**.

2.3 REGISTRATION PROCEDURES

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

will be forwarded electronically via e-mail to the research team. Voicemail is available during non-working hours.

2.4 RANDOMIZATION (OR STRATIFICATION) PROCEDURES:

Dr. Steinberg will create the randomization lists using variable block sizes. Patients will be randomized with a single stratification factor to try to ensure a balanced distribution among those getting placebo or not initially: being identified as having a high intensity of immunosuppression (2 or more agents/modalities ± prednisone≥0.5 mg/kg/day) vs. no or a lesser intensity of systemic immunosuppression according to the Intensity of Immunosuppression Scale[10].

Once patients have been evaluated and meet all eligibility requirements, patients will be registered with the NCI Central Registration Office and be randomized to either clobetasol or placebo. Change of systemic immunosuppressive regimen occurring after enrollment will not be allowed, and if this is necessary during the 2-week blinded phase of the study to control progressive systemic cGVHD, the patient will come off the study. Other medication changes will be documented at the interim or final (end of treatment) appointment and taken into consideration in the final analysis. However, given the small, pilot nature of the study, it is unlikely that the effect of all potential confounders can be meaningfully taken into account.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a randomized, double blind, placebo-controlled, pilot study of clobetasol 0.05% topical oral rinse with an open label cross-over or extension period. Consenting subjects with clinically significant oral chronic GVHD will be randomized to clobetasol 0.05% or placebo oral rinse. The placebo will be flavored with quinine, to approximate the “bitter” taste of clobetasol.

Subjects will be evaluated at bi-weekly intervals while on the study intervention. OMRS score will serve as the primary outcome measure. At the first 2 week interim appointment patients will be unblinded and started on the clobetasol oral rinse open label. In the absence of progressive oral disease on the scheduled interim evaluations during the 4-week clobetasol treatment period, all patients will complete a total of 4 weeks of treatment with clobetasol. Therefore, patients who were originally assigned to clobetasol arm will receive additional 2 weeks of treatment, and patients assigned to placebo arm will undergo an additional 4 weeks of treatment with clobetasol after unblinding. Patients with progressive disease after 2 weeks of therapy with clobetasol will be considered non-responders, taken off-treatment and treated as appropriate in consultation with primary clinician. Within 90 days of the end of the 1 month of treatment, all patients with evidence of benefit (response or stable disease) will be given an option to continue treatment with clobetasol 0.05% with or without additional treatment as deemed clinically necessary for 1 month after the conclusion of the initial treatment period. Additional follow-up appointment will be scheduled for all patients 1 month after completion of treatment. The change in OMRS scores from baseline to 4 weeks of mouth rinse usage will be the primary outcome variable. For the placebo group, the OMRS score at the end of the blinded phase/beginning of clobetasol rinse use (day 14) will serve as the baseline for the primary outcome. Difference in OMRS score between the groups (placebo and clobetasol) at the end of the 14-day blinded phase will serve as a secondary outcome measure. The study schedule of events is outlined in Appendix G.

Date: ____/____/____ Timepoint: _____ LIP print name: Jacqueline Mays LIP Signature:_____

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

Total _____

Date: ____/____/____ Timepoint: _____ LIP print name: Jacqueline Mays LIP Signature:_____

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

Total _____

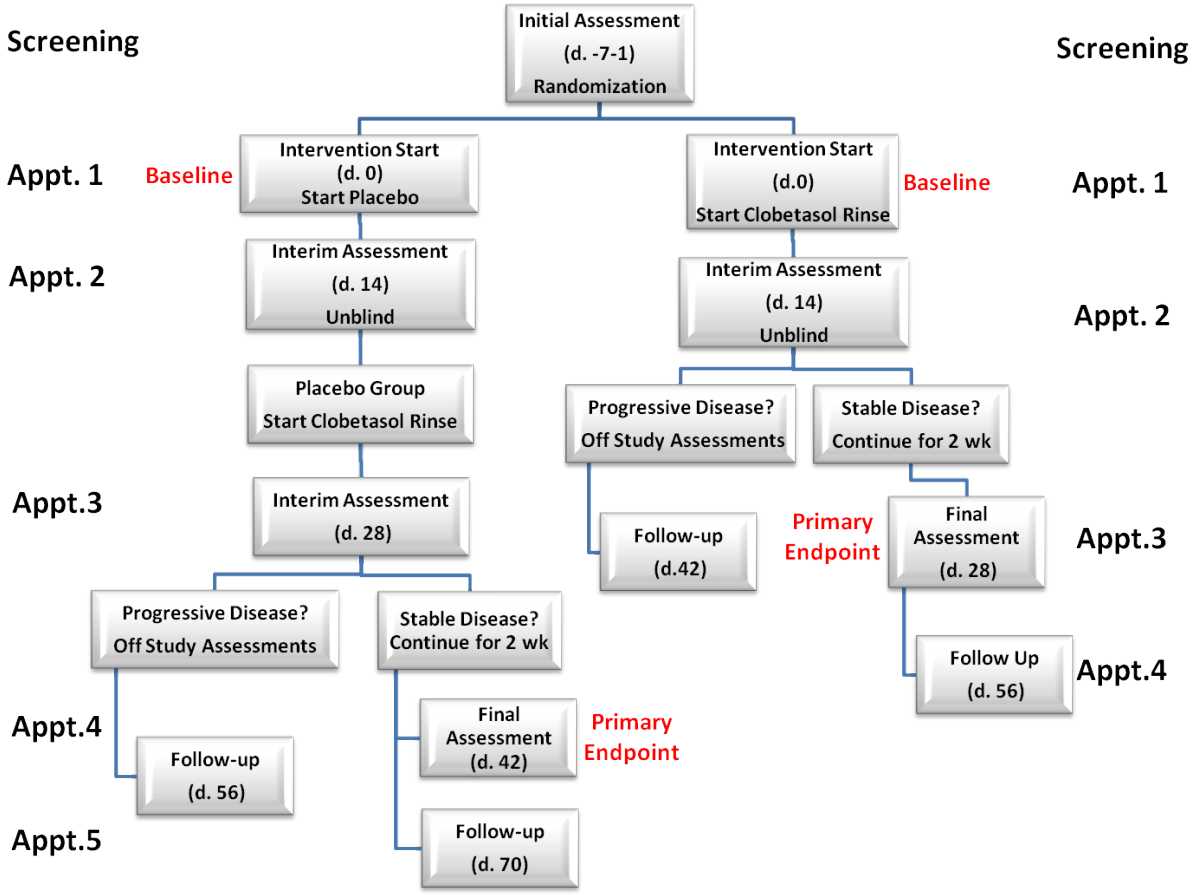
ate: ____/____/____ Timepoint: _____ LIP print name: Jacqueline
ays LIP Signature:_____

ecause **of problems with your teeth, denture or mouth have you…**	Never **(0)**	Hardly **ever (1)**	**Occasionally (2)**	**Often (3)**
ad trouble pronouncing words				
lt sense of taste has worsened				
ad painful aching in the mouth				
und it uncomfortable to eat any foods				
ave been self-conscious				
lt tense				
ad an unsatisfactory diet				
ad to interrupt meals				
und it difficult to relax				
ave been a bit embarrassed				
ave been irritable with other people				
ad difficulty doing usual jobs				
lt life in general was less satisfying				
ave been totally unable to function				

otal
_____

Appendix GFor pediatric patients (< 18 years of age at enrollment), ACTH stimulation test and oral biopsy will be done as clinically indicated, and are not required by the protocol. These procedures may still be done for clinical diagnostic and monitoring purposes.

3.1.1 Study Schema



3.2 DRUG ADMINISTRATION

3.2.1 Clobetasol Administration

Clobetasol 0.05% oral rinse and placebo rinse which will be identical in appearance and taste will be labeled and dispensed by the NIH Clinical Center Pharmacy. Subjects will be instructed to rinse oral cavity 3 times daily with the 10 cc of the study medication for 2 minutes and spit out and not to eat, drink, or brush teeth for 30 minutes after the study drug administration. Additionally, the use of oral topical analgesic (viscous lidocaine) will not be allowed for 30 minutes before and after study drug administration.

3.2.2 Duration of Drug Therapy

Patients will be treated with study medication for up to 4 weeks initially. If patients enter the continuation treatment period, they can be treated for up to an additional 4 weeks. Patients may be allowed to enter the continuation treatment period up to 90 days after the last day of treatment.

3.2.3 Progressive disease

Patients with progressive oral cGVHD after 2 weeks of treatment with the clobetasol oral rinse will be taken off study. See also Section **6.3.1**.

3.2.4 Treatment after 2 week blinded phase

Patients who switch to the clobetasol arm due to initial placebo assignment will be treated with clobetasol 0.05% oral rinse for 4 weeks. Patients originally assigned to clobetasol arm will be treated for another 2 weeks.

3.3 TREATMENT MODIFICATIONS

All dose modifications must be discussed with the PI, or LAI. Given favorable toxicity profile of clobetasol, no treatment modifications are expected. Grade 2 – 3 CTCAE v.4 events attributable to underlying disease and occurring prior to administration of clobetasol will not be reported as an adverse event. These physical findings must be documented at baseline. Expected pre-existing manifestations of cGVHD or systemic steroid therapy may include the following examples: fatigue, colitis, cushingoid appearance, anorexia, dyspepsia, xerostomia, parotid swelling, nausea, taste alteration, arthritis, fibrosis, myositis, osteonecrosis, osteopenia, dry eye, watery eye, pain, dyspnea, vaginal dryness, skin atrophy, alopecia, hyperpigmentation, skin dryness, hypopigmentation, nail changes, photosensitivity, pruritus, rash, and ulcers[12]. In the event of grade 2-3 adverse event attributable to study agent that cannot be easily alleviated without compromising the integrity of the study (such as severe local or systemic hypersensitivity) the subject will be taken off study and treated appropriately as detailed in Protocol Evaluations

3.3.1 Pre-Treatment Evaluation

Pre-treatment tests should be performed within 1 month prior to enrollment on the trial unless otherwise stated. Evaluation may be performed as part of 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.” All attempts will be made to enroll patients on this study; however evaluation may be done as part of any ongoing NCI protocol. A 7-day washout period is required if patients are currently using another oral topical treatment for mouth lesions.

1. Optional History and Physical Examination
2. NIH global scoring and data collection, including prior and concurrent therapy, (Appendix H)
3. Chronic GVHD NIH organ staging
4. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument (**Appendix A** and Appendix B**)**
5. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness

Appendix C)

6. Oral Global Scale (**Appendix D**)
7. Painometer (POM) Assessment (**Appendix E**)
8. Oral Health Impact Profile- OHIP-14 (**Appendix F**)
9. Hematology: Complete blood counts, with differential and platelet count. Within 72 hours prior to initial evaluation.
10. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, serum cortisol level and TBNK panel. Within 72 hours prior to initial evaluation.
11. FSH, LH, TSH, T4, CMV by PCR, and HSV by PCR.
12. Urine or Serum Pregnancy test: For all females of childbearing potential. This test is to be performed within 7 days prior to enrollment on the trial.
13. Urine glucose - Within 72 hours prior to initial evaluation.
14. Biopsy of buccal mucosa (4 mm punch) on patient's right side OR of buccal area with GVHD involvement for histopathological examination.
15. Research blood sample collection (18cc)
16. Five minute saliva sample, with and without paraffin stimulation
17. Short ACTH stimulation test, within 1 week prior to initial evaluation.
18. Clinical oral photo series
19. Adrenocorticotropic Hormone blood level within 1 week prior to initial evaluation.
20. Hemoglobin A1C level

3.3.2 Interim Evaluation

Patients should be evaluated at the NIH 14 days after the start of intervention until Day 28 of active rinse use for the following:

1. Optional History and Physical Examination
2. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument (**Appendix A** and Appendix B)
3. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness (**Appendix C**)
4. Oral Global Scale (**Appendix D**)
5. Painometer (POM) Assessment (**Appendix E**)
6. Oral Health Impact Profile- OHIP-14 (**Appendix F**)
7. Hematology: Complete blood counts, with differential and platelet count

8. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, cortisol level and TBNK panel.
9. Research blood sample collection (18cc)
10. Urine glucose
11. Five minute saliva sample, with and without paraffin stimulation
12. Clinical oral photo series
13. Optional pharmacokinetic study
14. Hemoglobin A1C level

3.3.3 End of Treatment Evaluation

The following tests and procedures should be performed at the end of scheduled open label treatment period (28 d.) or, if possible, at the time a patient comes off treatment regardless of the reason:

1. Optional History and Physical Examination
2. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument(**Appendix A** and Appendix B)
3. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness (**Appendix C**)
4. Oral Global Scale (**Appendix D**)
5. Painometer (POM) Assessment (**Appendix E**)
6. Oral Health Impact Profile- OHIP-14 (**Appendix F**)
7. Hematology: Complete blood counts, with differential and platelet count
8. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, HSV by PCR, cortisol level and TBNK panel.
9. Urine glucose
10. Research blood sample collection (18 cc)
11. Biopsy of buccal mucosa (4 mm punch) near baseline biopsy site
12. Five minute saliva sample, with and without paraffin stimulation
13. Clinical oral photo series
14. Short ACTH stimulation test
15. Adrenocorticotropic Hormone blood level
16. Hemoglobin A1C level

The goal of the day 28 biopsy is to assess microscopic and molecular changes associated with response (or lack thereof) to topical clobetasol for the purpose of potential cGVHD marker development. The primary response variable in this study is clinical grading of cGVHD.

3.3.4 Follow-up Evaluation

The following tests and procedures should be performed at the end of the scheduled follow-up period (28 days post end of open label treatment period):

1. Optional History and Physical Examination
2. Chronic GVHD NIH organ staging
3. Assessment of oral GVHD using OMRS and oral cGVHD Clinical Scoring Instrument (**Appendix A** and **Appendix B**)
4. Numeric rating scales for (0 to 10) for oral pain, oral sensitivity, and oral dryness (Appendix C)
5. Oral Global Scale (**Appendix D**)
6. Painometer (POM) Assessment (**Appendix E**)
7. Oral Health Impact Profile- OHIP-14 **(Appendix F**)
8. Hematology: Complete blood counts, with differential and platelet count
9. Chemistries: Electrolytes (including sodium, potassium, chloride, CO2, calcium, phosphorus and magnesium), creatinine, BUN, glucose, SGOT, alkaline phosphatase, SGPT, bilirubin, PT/INR and PTT, cortisol level and TBNK panel.
10. Research blood sample collection (18cc)
11. Five minute saliva sample, with and without paraffin stimulation
12. Clinical oral photo series
13. Hemoglobin A1C level
14. Short ACTH stimulation test (Per PI discretion at day 56 or day 70 depending on subject randomization group) if there is concern for endocrine side-effects)

3.4 Dose Modifications

No dose modifications are expected during this study.

3.5 Questionnaires

3.5.1 Oral Mucositis Rating Scale

Description. The OMRS was constructed through the careful selection of clinical descriptors of oral mucosal changes related to GVHD and also related to BMT[16]. The OMRS was developed "…as a research tool for the comprehensive measurement of a broad range of oral tissue changes associated with cancer therapy" and "to develop an index for assessing acute oral mucositis after BMT[36]". Preliminary development of this scale was performed in studies of chemotherapy toxicities and cGVHD and use of the tool allowed "expedient, efficient, detailed, and reproducible classification of oral changes[36]". The OMRS was used by Schubert, Sullivan, Morton et al. (1984) with 60 patients, who were 180 to 500 days after ABMT, to determine if late oral abnormalities were associated with the presence of cGVHD. Oral manifestations found to be most strongly associated with cGVHD included atrophy and erythema or lichenoid lesions of the buccal and labial mucosa and oral pain[16].

The tool divides the oral cavity into seven distinct anatomic areas: lips; labial and buccal mucosa; tongue; floor of mouth; palate; and attached gingiva. Each site is further divided into upper and lower (lips and labial mucosa), right and left (buccal mucosa), dorsal, ventral, and lateral (tongue), and hard and soft (palate). Descriptive categories include atrophy, pseudomembrane, erythema, hyperkeratosis, lichenoid, ulceration, and edema. Erythema, atrophy, hyperkeratosis, lichenoid, and edema are rated on scales of 0 to 3 (0 = normal/no change, 1 = mild, 2 = moderate, and 3 = severe change). Ulceration and pseudomembrane are rated on scores based on estimated surface area involved (0 = none, 1 = ≥ 0 but ≤ $1cm^2$, 2 = ≥ $1cm^2$ but ≤ $2cm^2$, and 3 = ≥ $2cm^2$). The item pool consists of 91 items for 13 areas of the mouth that are assessed for several types of changes. The score is obtained by summing the scores of all items on the OMRS to yield a total possible score ranging from 0 to 273.

3.5.2 Painometer

Description. Pain will be self-assessed by subjects using a paper version of the Painometer , contains a visual analogue scale (VAS) to rate overall intensity of pain and a list of 14 sensory and 11 affective pain descriptors ranked by intensity values from 1 to 5 (POM-WDS)[37]. The POM is capable of capturing the multidimensionality of the pain experience. Patients are asked to look at the list of sensory and affective words (POM-WDS) and select sensory and affective words that describe their pain. The weighted scores assigned to the selected words are added together to obtain a pain intensity score for the sensory as well as for the affective components. The weights assigned to the words are derived from research involving people with various ethnic and educational backgrounds[37]. A vertical 10cm VAS (POM-VAS) is located on the POM with a centimeter scale allowing for overall pain intensity quantification. The POM-VAS is anchored with the words “no pain” located at the bottom of the scale and the words “worst possible pain” located at the top representing the extreme limits of pain. The patient is requested to circle a number indicating the amount of pain being experienced at the present time. The pain intensity score for the POM-VAS has a range of 1 to 10.

The affective and sensory pain scores are obtained by adding all of the respective intensity values. The range of possible sensory scores is from 0 to 48 and the range of possible affective scores is from 0 to 37. The sensory and affective scores may be added together to obtain the total pain intensity score for the POM-WDS, which may range from 0 to 85.

In a psychometric study that employed correlational and comparative designs, the test-retest reliability and the concurrent and construct validity of the POM-VAS and the POM-WDS were assessed in 279 patients with acute or chronic pain[37]. The following time intervals were used for data collection using the POM: labor pain- admitted to labor and delivery, cervical dilation at 2 to 4 cm x 2 with a 10-minute interval, cervical dilation at 5 to 7 cm and again at 8 to 10 cm, immediately prior to epidural block, and another 30 minutes after epidural block; post-operative pain-4 hours after the patients were admitted to the recovery room after surgery, each time the patient complained of pain, and routinely every 4 hours, prior to and after pain medication was given; chronic pain in RA patients on two occasions with a 2-hour interval between each pain measurement. Relatively high correlations were found between initial and repeat intensity ratings for the POM-VAS ($r = .88$, $p < .001$). Test-retest reliability of the POM-WDS ranged from .68 ($p < .001$) to .73 ($p < .001$) in RA patients, from .80 ($p < .001$) to 0.84 ($p < .001$) in labor patients, and from .70 ($p < .001$) to .74 ($p < .001$) in postoperative patients. Concurrent validity of the POM-WDS was supported by correlations between the POM-WDS and the McGill Pain Questionnaire ($r = .069$, $p < .001$) and POM-VAS ($r = .85$, $p< .001$). Construct validity evidence

was gathered for the POM by showing that pain scores decreased significantly for POM-WDS ($t = 5.53$, $p < .001$), and POM-VAS ($t = 6.18$, $p < .001$) after the patients had received pain medication. A correlation between the traditional paper-and-pencil VAS and the POM-VAS was reported to be 0.98 ($p < .001$).

A modified Gaston-Johansson Painometer Assessment Sheet will be used to record the following data regarding stomatitis-related acute oropharyngeal pain experienced at rest and with swallowing: intensity; sensory and affective descriptive words from the POM-WDS; duration (continuous or periodic).

3.5.3 Visual analogue scales for subject reported oral pain, oral sensitivity, and oral dryness

Subject reported oral pain, oral sensitivity, and oral dryness will be captured through use of a 0 to 10 visual analogue scale (VAS) anchored with the words "no pain" to "worst pain" (Appendix C). We will use this VAS to evaluate these symptoms over treatment.

3.5.4 Global Rating Scale (perception of changes in oral condition)

At the interim and final visits, we will assess patients' perceptions of the changes in the oral condition on a 5 item scale (worsened greatly, worsened somewhat, stayed the same, improved somewhat, improved greatly). The data will be correlated with the results from the numerical scoring systems to assess internal validity (**Appendix D**).

3.5.5 Oral Health Impact Profile–14

Oral Health Impact Profile–14 (OHIP-14, **Appendix F**) is a 14 item questionnaire developed to assess the state of oral health as perceived by a patient [38,39]. Increased use of patient centered outcome measures has been advocated in the recent years. Patient centered outcome measures complement objective measures to provide a more complete picture of the impact of disease and treatment. OHIP-14 has been used in oral disease studies including oral lichen planus (a dermatological condition with manifestation similar to chronic oral GVHD). It has been shown to have high validity and reliability, and to be sensitive to treatment effects.

3.6 Study Calendar

See also **Appendix G**.

3.6.1 Compliance

Subject adherence to the trial interventions will be estimated by measuring the volume of the remaining study medication at follow up appointments, study medication use diaries (**Appendix I**) and compliance with clinic visits. Correct use of the study medication will be demonstrated at the beginning of the study. Reinforcement such as periodic phone calls by the study nurses will be used to maximize compliance.

3.7 Duration of Follow- Up

Patients will be followed for 6 months total after discontinuing clobetasol oral rinse treatment every 3 months by telephone or in-person interview to assess duration of treatment response, recurrence of oral GVHD, survival and resolution of any side-effects. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Once there is resolution of adverse events, patients will be removed from study. Patients who become unavailable within 6 months of completing treatment will not be followed

beyond the terminating event. Only adverse events at least possibly related to study treatment will be collected during the follow-up period.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

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

3.8.1 Criteria for removal from protocol therapy

- Progressive oral cGVHD after 2 weeks of treatment with clobetasol: Patients will be unblinded at the time of GVHD progression and taken off treatment.
- Unacceptable toxicity: we do not expect significant adverse events associated with the study medication or procedures. In the event of unexpected toxicity attributable to the study drug (grade 2 or greater) patients will be taken off treatment.
- Change in the systemic immunosuppressive therapy while in the 2 week blinded phase
- Patient requests to stop therapy
- Investigator discretion

3.8.2 Off-Study Criteria

- Progressive oral cGVHD after 2 weeks of treatment with clobetasol: Patients will be unblinded at the time of GVHD progression and taken off study as defined in Section **6.3.1**.
- Unacceptable toxicity: we do not expect significant adverse events associated with the study medication or procedures. In the event of unexpected toxicity attributable to the study drug (grade 2 or greater) patients will be taken off study.
- Patients unable to comply with study requirements will come off study. This includes ≥75% non-compliance with study oral rinse usage.
- Patients will come off study upon completion of follow-up Period (6 months after discontinuing clobetasol oral rinse treatment).
- Death
- Patient lost to follow up
- Patient withdrawal from follow-up period
- Change in the systemic immunosuppressive therapy while in the 2 week blinded phase
- PI decision to end this study

3.8.3 Off-Study Procedure

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

4 SUPPORTIVE CARE

Supportive care will be provided as specified in the primary transplant protocol and may include standard infection prophylaxis, anti-emetics, CMV surveillance at follow-up, topical care including topical analgesics, physical therapy, nutritional, and psychosocial support per NIH Blood & Marrow Consortium Supportive Care Guidelines (http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml). Anti-emetic therapy should not include dexamethasone or other corticosteroids.

4.1 CONCURRENT THERAPY

Topical corticosteroid treatment is associated with few potential complications. The most common is overgrowth of oral candidiasis. Many but not all patients with chronic GVHD are already taking antifungal prophylaxis such as oral fluconazole. Thus, to reduce incidence of oral candidiasis infection, patients will be asked to swish and spit once per day with nystatin (100,000u/ml) rinse, which is a standard preventative measure in high-risk patients. In case oral candidiasis develops, standard therapy according to NIH Consortium guidelines (http://intranet.cc.nih.gov/bmt/clinicalcare/guidelines.shtml) with topical or systemic antifungals will be administered.

The use of additional topical or systemic immunosuppression is prohibited during the study period and should be avoided if possible during the cross-over/extension period. Other topical agents (oral or skin), are prohibited with the exception of topical viscous lidocaine supplied by the NIH pharmacy. However, the change in the systemic immunosuppressive medications will not be allowed while on the blinded phase of the study and will be avoided, if possible, on the open label phase. If the absolute necessity develops to change or increase the systemic immunosuppressive therapy while in the blinded phase (e.g. for progressive GVHD in the organ sites other than oral cavity), patients will be taken off-study. Topical analgesic solution, available in NIH pharmacy (viscous lidocaine) will be permitted for control of oral discomfort. Other topical analgesics or mouthwashes will not be allowed. All interventions and medications dictated by the subject's primary transplant protocol and clinical necessity, including systemic analgesics, will be permitted. Subjects will keep daily records reflecting topical and systemic analgesic use (**Appendix I**). Factors that can potentially confound the results (such as change in systemic steroids and other immunosuppressants) will be taken into consideration in the final statistical analysis.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

5.1.1 Biologic Studies

Adult patients will have no more than 10.5 ml/kg or 550 ml peripheral blood, whichever is smaller, drawn in 8-week study period for research studies. Children under 18 years of age will have no more than 9.5 ml/kg drawn in 8-week study period for research studies. These guidelines are according to The Clinical Center Policy and Communications Bulletin M95-9.

5.1.2 Additional Analyses

Note: All samples will be sent for storage until analysis as detailed in Section **5.2** under appropriate storage conditions.

The oral tissue sections will be examined by a pathologist to assess oral cGVHD status. Half of the biopsy will be formalin-fixed and sent to pathology for H&E staining. One quarter will be flash frozen for analysis of gene expression, and one quarter will be frozen in OCT media, and both quarters will be stored until analysis. Immunohistochemical and PCR analysis will focus on characterization of cellular infiltrate, inflammatory cytokines, chemokines and protein mediators present at baseline and after clobetasol treatment.

Whole saliva samples will be examined for evidence of disease-related biomarkers associated with cGVHD and clobetasol treatment. Saliva will be collected in two 5-minute periods, one unstimulated and one stimulated with inert chewing (paraffin wax)[32]. The volume collected will be compared and used to indicate gland function[32].

Blood samples will be used to measure cortisol levels and in a subset of samples, to determine blood levels of clobetasol during treatment with the mouth rinse formulation. Heparinized plasma and cells will be stored for potential analysis of inflammatory markers and cellularity associated with cGVHD and clobetasol treatment.

One plasma sample (6 ml) will for LC-MS-MS analysis for clobetasol content.

5.1.3 Pharmacokinetic Studies

To determine if and how much clobetasol is absorbed through the oral mucosa in these cGVHD patients, blood levels of clobetasol (6 ml sample) will be monitored at baseline, 2- and 4-weeks of clobetasol rinse use. A random subset of half of the subjects (expected n=17) will be initially assessed for clobetasol plasma concentration. The determination of clobetasol concentrations in plasma samples, as well as the pharmacokinetic data analysis, will be performed by the Clinical Pharmacology Program. Samples will be analyzed using a validated LC-MS/MS method developed at the end of the trial. If this data indicates a positive correlation between plasma clobetasol level and the other study measures of adrenosuppression (ACTH stimulation test, morning cortisol levels), or if we see either unexpected clinical or surrogate responses, or wide variability in levels, the analysis will be extended to all study patients.

In a subset of consenting patients (up to n=10), the pharmacokinetics of clobetasol 0.05% mouth rinse will be assessed in a single session. After one two-minute oral rinse use, a venous blood sample will be collected in a 6 ml sodium heparin (green top) tube (BD Sodium Heparin 367878 or 367879) at x0, x15-45 and x90-120 minutes. The plasma clobetasol levels from these samples will be used to analyze the basic pharmacokinetics of clobetasol 0.5% oral suspension. Participation in this part of the study is optional, and a separate section has been included on the consent form to allow patients to elect participation or not. The first 10 patients who consent for the pharmacokinetics study will be selected for sampling.

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

5.2.1 Sample Procedures

The saliva, blood and tissue samples, collected for the purpose of research under IRB approved protocols of the Experimental Transplantation and Immunology Branch (ETIB)/Immune

Deficiency Cellular Therapy Program (IDCTP) will be stored and may be archived by the Biospecimen Processing Core (BPC), with the exception of blood samples for clobetasol analysis, which will be stored separately by the Clinical Pharmacology Program (CPP) until analysis. These will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

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

Barcoded samples are stored in locked freezers at -20 or -80°C (sera and plasma) or under liquid nitrogen (cells), or as otherwise applicable according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

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

5.2.2 Protocol Completion/Sample Destruction

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

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed or returned to the participant, if so requested. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of Section **7.2**.

5.2.3 Sample Processing

The determination of clobetasol concentrations in plasma samples, as well as the pharmacokinetic data analysis, will be performed by the Biospecimen Processing Core (BPC). A venous blood sample will be collected in an 8ml SST tube to be processed for serum. Record the date and exact time of draw on the tube.

Please email Clinical Pharmacology Blood Processing Core (BPC) at NCIBloodcore@mail.nih.gov at least 24 hours before the scheduled research blood draw time and before patient treatment start times (the Friday before is preferred).

For sample pickup, page **102-11964**.

For immediate help, call the main line for the BPC at (240) 760-6180. If no answer, call the main clinical pharmacology lab phone number at (240) 760-6190.

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

The samples will be processed, barcoded, and stored in Dr. Figg's lab until requested by the investigator.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

6.1.1 Data Collection

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR 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. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

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

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

Grade I AEs will only be recorded if they are deemed possibly, probably or definitely related to the study intervention.

6.1.2 Eligibility Checklist

To be completed at study entry and forwarded to protocol research nurse.

6.1.3 Protocol Deviations

Any protocol deviations should be directly reported to the PI or LAI.

6.2 ORAL GVHD SEVERITY SCALES

The primary endpoint will be evaluated using expanded oral GVHD severity scale (**Appendix A**)[33,34]. There is no standard definition of response in this field. The definitions we will use in this pilot study to grade the level of response to study intervention will be as follows:

- **Progression (PD):** defined as increase of 25% of initial score (rounded to the closest number) on the OMRS scale (**Appendix A**).
- **Partial Response (PR):** defined as decrease of 25% of initial score (rounded to the closest number) on the OMRS scale (**Appendix A**).
- **Complete Response (CR):** defined as score of 0 on the erythema and ulceration components of the OMRS scale (**Appendix A**).
- **Stable Disease (SD):** does not meet criteria for progression or response.

For the purpose of OMRS instrument evaluation validation, we will also use a simplified scale developed for assessment of cGVHD response in the oral cavity (Appendix B)[35]. Scoring will be performed by investigators trained in assessment of oral cavity lesions. As part of the evaluation

of the scales, the results will be correlated with scores from symptom-oriented instruments and global scale.

6.3 RESPONSE CRITERIA

6.3.1 Response Criteria

The primary endpoint will be evaluated by using the OMRS (**Appendix A**). Secondary endpoints will be assessed using scales for oral discomfort and xerostomia, patient-reported global scale, and oral cavity specific quality of life questionnaire (OHIP-14).

6.4 TOXICITY CRITERIA

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

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem or present new information that might affect the willingness of participants to enroll or remain on the study will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

Serious adverse events potentially attributable to the study medication or procedures will be reported to IRB. If trends are noted and/or risks warrant it, accrual will be interrupted and/or the protocol and/or consent document will be amended accordingly.

7.4.1 Principal Investigator/Research Team

The clinical research team consisting of the PI, LAI, research nurse and data manager will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient, data acquisition, approve CRFs for data entry and address any other logistical issues pertinent to the integrity of the protocol implementation and data management.

All data will be collected in a timely manner and reviewed by the Principal Investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in Section **7.2.1** will be submitted within the appropriate timelines.

The Principal Investigator will review adverse event and response data on each participant 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.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2)).

8.1.2 Serious Adverse Event (SAE)

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

- Death,
- A life-threatening adverse event (see Section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.

- A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
- Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version [X].

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site Principal Investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as

the site Principal Investigator or sub-investigator.

- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site Principal Investigator or sub-investigator.

For timeframe of recording adverse events, please refer to Section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in Section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in Section **8.4**.

All SAE reporting must include the elements described in Section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://nih.sharepoint.com/:u:/r/sites/NCI-CCR-OCD-Communications/SitePages/Forms-and-Instructions.aspx?csf=1&web=1&e=uWBXtI

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Regulatory Reporting for Studies Conducted Under CCR-Sponsored IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

8.5 Sponsor Protocol Deviation Reporting

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol

deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

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

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

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 SUBJECT ACCRUAL

Subjects of both sexes, from all racial and ethnic groups are eligible for this trial if they meet the criteria outlined in Section 2.1. To date, there is no information that suggests differences in drug metabolism or disease response among racial or ethnic groups or between the two sexes, indicating that results of the trial will be applicable to all groups. Efforts will be made to extend the accrual to a representative population, but achievement of a fully representative subject population is unlikely in a pilot study with limited accrual.

10.2 STATISTICAL CONSIDERATIONS

The primary objective of this randomized pilot study is to determine if the use of clobetasol may result in improvement or stabilization in outcomes in patients with oral chronic GVHD. An important secondary objective is to preliminarily validate and explore the utility of the response measurement instruments.

Patients with oral cGVHD meeting the eligibility criteria will be separately randomized to either 1 month of clobetasol 0.05% oral rinse or placebo; there will not be separate accrual goals for each age group or type of underlying disease. The patients will be followed every 2 weeks for 1 month for their primary endpoint, and once 1 month after completion of study agents.

The primary endpoint will be the change in OMRS score (**Appendix A**) after 1 month of clobetasol 0.05% oral rinse compared to baseline. We will consider a 25% or larger decrease in the score to be clinically significant and a 'response' for the purpose of this study. As this is a pilot study, the association between this level of change and other scales will also be assessed to determine if this is a meaningful measure to use in future trials or if modification is warranted. Thus, this study will be a pilot for the determination of a meaningful response as well for determining if the agent tested may be beneficial.

After the first 2 weeks of clobetasol treatment, patients can be removed from study if oral disease progression is documented. Patients who are taken off study for oral disease progression will be counted as non-responders at the time of the final analysis. Patients taken off study for non-compliance, specifically ≥75% non-use of the oral rinse, will not be included in the data analysis

The patients enrolled on this study may be a very heterogeneous group with respect to prior treatments, extent of disease, etc. Patients taken off study for reasons unrelated to the primary outcome will be classified as non-responders and analyzed accordingly. The results will be interpreted in the context of a pilot study with potential limitations noted.

This study will aim to enroll a total of 34 evaluable patients randomized in a 1:1 fashion (17 per arm) to receive clobetasol rinse or placebo. The initial phase of the study will involve two weeks of either clobetasol rinse or placebo. At the end of the initial 2 weeks, patients receiving placebo will receive 28 days of clobetasol while those receiving clobetasol initially will receive an additional 14 days of clobetasol. Thus, each group will receive 28 days of clobetasol following either a 14 day placebo or immediately after randomization.

Patients will be randomized with a single stratification factor to try to ensure a balanced distribution among those getting placebo or not initially: being identified as having a high intensity of immunosuppression (2 or more agents/modalities ± prednisone≥0.5 mg/kg/day) vs. no or a lesser intensity of systemic immunosuppression according to the Intensity of Immunosuppression Scale [10]. This scale was developed using expert opinion, and has been preliminarily demonstrated to have predictive validity as measure of the intensity of systemic immunosuppression[10,40]. A low intensity regimen is defined as treatment with prednisone alone at a dose of less than 0.5 mg per kilogram per day. Moderately intense regimens include single agent prednisone at a dose greater than or equal to 0.5 mg per kilogram per day, and/or any other single agent or modality. Regimens comprised of two or more agents or modalities (+/- prednisone greater than or equal to 0.5 mg per kilogram per day), are categorized as highly intensive systemic immunosuppression. When scoring the intensity of systemic immunosuppression, the use of topical agents is not captured.

The primary endpoint is the fraction of subjects who experience a 25% improvement in their OMRS compared to their own baseline. The fraction will be estimated with a two-tailed 95% confidence interval as the primary outcome. This will be done using all 34 patients together provided that the changes from baseline to day 28 for the two groups are sufficiently similar. A formal test will be performed assess their comparability. This will be determined conservatively, by obtaining the actual difference in the individual OMRS for each patient at baseline (day 0 for initial clobetasol and day 14 for those initially given placebo) vs. the value after day 28 of clobetasol and comparing those differences between the two randomized groups using a two-tailed Wilcoxon rank sum test. If the p-value for that comparison is >0.30, then the two groups will be considered sufficiently similar to allow pooling of the results and to report a combined

fraction of patients who have a 'response' to 28 days of clobetasol. In this case 34 patients will be sufficient to allow the proportion of patients with a response of 75% or more to have a two-sided 95% confidence interval of +/- 15% or less, which will be considered sufficiently precise. Fractions of responses <75% would have slightly wider confidence interval widths.

An important secondary endpoint is to compare the changes from day 0 in the OMRS until day 14 between those who only receive placebo by that point vs. those who received clobetasol. This evaluation will be done both with respect to the fraction with a response by 2 weeks, as well as comparing the actual changes in OMRS from day 0 to day 14.

By enrolling 17 patients per arm, a 0.10 alpha level one-tailed Fisher's exact test will have 80% power to detect a difference between a potential 75% of patients having a 25% or greater decrease in severity score on the clobetasol arm and about half that amount, 35%, on the placebo arm. A one-tailed test is sufficient for this secondary objective in this study since we will not expect clobetasol to be associated with a lower fraction of patients with benefit compared to placebo and because this is intended to be a pilot study to determine if a potential trend of magnitudes anticipated, but not necessarily a statistically significant gain, may be detected. Should very promising results be obtained, then a subsequent trial could be conducted to build upon and further confirm the benefit noted.

A comparison of the actual levels of changes in the oral severity score between the arms will also be done using a Wilcoxon rank sum test as a secondary analysis. With 17 patients per arm, there is approximately 80% power to detect a difference between the arms in the changes from baseline to day 14 equal to one standard deviation of the change (effect size=1.0), using a two-tailed Wilcoxon rank sum test with a 0.05 significance level.

All patients will be placed on clobetasol for one month, whether following a two-week period with placebo or beginning at the time of randomization. In addition, comparisons between actual oral severity scores at the beginning of this period and one month later will be made using a paired t-test, or using a Wilcoxon signed rank test if the differences are not normally distributed ($p<0.05$ by Shapiro-Wilks test). These results will be evaluated separately according to the randomized treatment arm as well as overall if the changes in score according to the randomized assignments are similar ($p>0.30$ for Wilcoxon rank sum test comparing changes in scores between the two arms over the one month clobetasol period). Although this would also be considered a secondary evaluation, there would be 82% power to identify a 0.75 standard deviation change to be significant with a two-tailed 0.05 alpha level paired t-test if all 17 patients are available within each arm for this comparison.

Patients will undergo oral mucosa biopsies at the beginning of the study, and many are expected to have biopsies at the end of 28 days of treatment. Although required, these biopsies may not be obtained on all patients, and the number of patients with paired data will determine the differences in immunologic parameters from the biopsies that can be detected. For example, if there were 20 patients with paired biopsy data and 5 immunologic parameters of interest, each one would have 93% power to detect a change with an effect size of 1.0, with a very conservative two-tailed 0.01 significance level, to account for multiple comparisons. Fewer than 20 patients with paired biopsies would reduce the power accordingly, but since this is a secondary objective, the results of these tests will be presented in the context of an exploratory study.

At a rate of 1 patient per 2 weeks accrual, approximately 16 to 20 months will be required to meet the accrual goal of 34 evaluable patients. To allow for a small number of inevaluable patients, the accrual ceiling will be set at 40 patients.

11 HUMAN SUBJECTS PROTECTIONS

11.1 RATIONALE FOR SUBJECT SELECTION

No subjects will be excluded from participation based on sex, race or ethnicity. The study will be open to all subjects who satisfy the inclusion criteria and provide an informed consent to the protocol. From previous transplant protocol recruitment patterns at NIH we expect that over 80% of patients in this study will be adults over 18.

Recruitment: Subjects will be primarily recruited from NIH Clinical Center hematopoietic stem cell transplant clinics but could be referred from the outside institutions.

11.2 PARTICIPATION OF CHILDREN

This study will be limited to subjects aged 12 or older. Given the preliminary nature of the study and requirement for precise compliance with the instructions to minimize swallowing and systemic absorption of clobetasol, children < 15 who are less likely to comply will be excluded. In addition, due to the risk of swallowing, oral rinses such as topical fluorides are not recommended for young children.

11.3 PARTICIPATION OF NIH SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **11.5**), all subjects ≥ age 18 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.

11.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

11.4.1 Related to Clobetasol

The side-effects of topical steroids are usually limited to Candida (yeast) infection. This is relatively uncommon in our patient population (<5%), easily treatable and does not require discontinuation of the treatment. Low levels of topical steroids are absorbed through the oral mucosa, but the exact rate is not known. While adrenal suppression is very rare with topically applied corticosteroids, it is physiologically possible. Cases of adrenal suppression following topically-applied steroid creams have been reported with long-term use on extensive body surface primarily in young children. In other reports, it was difficult to determine if there was adrenal suppression. Symptoms of adrenal suppression are non-specific and include fatigue,

nausea and abdominal discomfort. Since these symptoms are extremely common in the general hospital population, routine monitoring in the context of this study is not indicated. In this study, blood pressure and serum cortisol will be monitored at every visit, and adrenal function will be assessed at baseline and at the end of the study. Given the short duration of this study, we do not expect significant side effects. We will use blood pressure, urine glucose, blood cortisol, and a baseline and repeat ACTH stimulation test at day 28 of clobetasol oral rinse use to monitor systemic steroid exposure. In the highly unlikely event of significant adrenal suppression as assessed by repeat ACTH stimulation test, Clinical Center Endocrinology Service will be consulted and subject will be placed on the standard oral hydrocortisone taper.

Topical steroid treatment may allow for local reactivation of viral infections, including but not limited to HSV. Patients will be monitored for oral HSV by PCR at the baseline and Day 28 visits.

11.4.2 Related to Blood Collection

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

11.4.3 Related to Tissue Biopsy

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

11.4.4 Related to Pregnancy

Many post-transplant patients are not expected to become pregnant since ovarian failure is common in women after transplant. Women who are able to become pregnant will be expected to use an effective method of birth control. Although clobetasol will be applied topically in the mouth in this study, there is no way of knowing how much medication will be absorbed into the bloodstream. Strong corticosteroids have caused birth defects in animals.

11.5 RISKS/BENEFITS ANALYSIS

11.5.1 For Adult Subjects

Post-transplant patients require monitoring for post procedure complications. Although this monitoring represents a minor increase over minimal risk monitoring is medically indicated. The risks of participating in this trial are limited to side-effects of clobetasol and the risks of standard diagnostic procedures (oral mucosal biopsy, plasma collection). Subjects may receive direct health benefits from participation in this protocol due to additional clinical monitoring such as thorough oral examination for oral GVHD. In addition, subjects on the active medication arm may receive direct benefit from treatment of oral GVHD.

This companion protocol to the primary transplant protocol requires the collection of an additional blood sample for research purposes only. Samples will be collected during sample collection procedures that are part of their routine standard therapy.

Therefore this study meets the DHHS Regulations 45 CFR § 46. criteria for “more than minimal risk to subjects with prospect of direct benefit to individual subjects”.

11.5.2 For Pediatric Subjects

This study meets the DHHS Regulations as follows:

"The risk represents a minor increase over minimal risk". The risks of participating in this trial are limited to side-effects of clobetasol and the risks of standard diagnostic procedures (oral mucosal biopsy, plasma collection). Post-transplant patients require monitoring for post procedure complications. Although this represents a minor increase over minimal risk, said monitoring is medically indicated. This companion protocol to the primary transplant protocol requires the collection of additional blood samples for research purposes only. Oral biopsy is optional for the pediatric patients and will be performed only for clinical indications to rule out alternative diagnoses at enrollment and part of the tissue will be saved for research purposes.

"The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations." Post-transplant patients who enroll in this protocol are familiar with blood collection and hospital procedures due to their frequent need for monitoring for their primary disease and for post-transplant complications. The monitoring that will be done is in line with the monitoring that would be done post-transplant.

"The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition." The generalizable knowledge would include the collection of information about the features of their post-transplant complication and the possible discovery of an effective treatment of oral GVHD for pediatric patients in the future.

Subjects may receive direct health benefits from participation in this protocol due to additional clinical monitoring such as thorough oral examination for oral GVHD. In addition, subjects on the active medication arm may receive direct benefit from prevention of oral GVHD.

"Adequate provisions are made for soliciting assent of the children and permission of the parent or guardian, as set forth in § 46.408." Only adult patients or pediatric patients via their guardians who satisfy the previously described inclusion/exclusion criteria and understand and have given informed consent and assent may enroll in the protocol. Some of the participants in this protocol will be children (less than 18 years of age). In these cases, full and informed consent must be obtained from the parent or the legal guardian and an assent obtained from the child. If the child does not wish to participate in the study, then enrollment of the child into the study is prohibited. Importantly, any subject who enrolls in the protocol has the option of withdrawing from the protocol at any time.

Therefore, the protocol meets 45 CFR § 46.406 criteria for "a minor increase over minimal risk to subjects with prospect of direct benefit to individual subjects".

11.6 Consent and Assent Process and Documentation

The investigational nature and research objectives of this trial, the procedure and its attendant risks and discomforts will be carefully explained to the patient or the patient's parents or guardian if he/she is a child, and a signed informed consent document will be obtained prior to entry onto the study. The potential subject will be educated regarding the nature of the condition, proposed intervention, and outcome measures. Study subjects will be informed that participation is entirely voluntary and that withdrawal from the study can be made at any time

without penalty of benefits to which they may be entitled. Informed consent will be obtained by Dr. Jacqueline Mays, Dr. Steven Pavletic or an associate investigator of this protocol.

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Written assent will not be obtained from children as the study holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research. Verbal assent will be obtained as appropriate for children ages 12-17 and the parent or guardian will sign the designated line on the informed consent attesting to the fact that the child has given assent. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

At any time during participation in the protocol that new information becomes available relating to risks, adverse events, or toxicities, this information will be provided orally or in writing to all enrolled or prospective patient participants. Documentation will be provided to the IRB and if necessary the informed consent amended to reflect relevant information.

The investigators are requesting a waiver from the IRB to allow only one parent to sign the informed consent to enter a child on the protocol. Because many patients must travel to the NIH from long distances at substantial expense, requiring both parents to be present for the consent process could be a financial hardship for many families. When guardianship status of the child is uncertain, a social worker will be asked to investigate and, if necessary, seek documentation of custody status.

In situations where there is joint custody of a child, both parents must sign consent. If only one parent can be present at NIH, the other parent's consent can be obtained by telephone via the procedure described in Section **11.6.1**.

11.6.1 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.

11.6.2 Informed consent of Spanish speaking subjects

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

11.6.3 Short form consent process for other non-English speaking patients

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

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). 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.

12 REGULATORY AND OPERATIONAL CONSIDERATIONS

12.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

12.2 Quality Assurance and Quality Control

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13 PHARMACEUTICAL INFORMATION

13.1 CLOBETASOL ORAL RINSE

Other: Clobetatasol propionate, Temovate

Classification: Corticosteroid

Action: Anti-inflammatory and Immunosuppressive. Clobetasol is a high-potency corticosteroid with mainly glucocorticoid activity;

Supply / Availability: Commercially available in powder form (Spectrum Chemicals). The commercial supply will be prepared as a 0.05% oral rinse and labeled as study drug specific to this protocol by the Pharmaceutical Development Section of the NIH CC Pharmacy.

Product description: Clobetasol oral rinse 0.05% (500mcg/mL) is a clear, colorless solution

Active Ingredient: clobetasol propionate

Preparation: The commercially available clobetasol powder will be dissolved in the diluent, hydroxypropylated cyclodextrin in water, then methylparaben, propylparaben and ascorbic acid will be added. Oral rinse will be repackaged in an 8 ounce amber bottle and relabeled as study drug for the purposes of this study and to allow blinding of the patient, clinical staff, and investigators.

Storage: Store at room temperature (20^{o} to 25^{o}C (68^{o} to 77^{o}F) (see USP controlled room temperature.

Administration: Rinse oral cavity for 2 minutes and spit out. Use 3 times daily: after breakfast, lunch and before bedtime. DO NOT SWALLOW. Do not eat or drink for 30 minutes after use.

Dose: 10 mL (5mg)

Toxicities: see Section **6.4**.

13.2 STUDY PLACEBO ORAL RINSE

Supply: The placebo oral rinse will be prepared by the Pharmaceutical Development Section of the NIH Clinical Center Pharmacy and labeled as study supply for purposes of this study and to allow blinding of patients, clinical staff, and investigators.

Product Description: The placebo oral rinse contains the following ingredients: hydroxypropylated cyclodextrin, methylparaben, propylparaben, ascorbic acid, quinine, and water for injection.

Storage: Store at room temperature (20^{o} to 25^{o}C (68^{o} to 77^{o}F) (see USP controlled room temperature.

Administration: Rinse oral cavity for 2 minutes and spit out. Use 3 times daily: after breakfast, lunch and before bedtime. DO NOT SWALLOW. Do not eat or drink for 30 minutes after use.

Dose: 10 mL

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15 APPENDICES

15.1 APPENDIX A: ORAL MUCOSITIS RATING SCALE (OMRS)

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

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

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

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

Rating Criteria

Change is rated from normal

Atrophy, erythema, hyperkeratosis, lichenoid , and edema

0 = Normal/No change
1 = Mild change
2 = Moderate change
3 = Severe change

Ulceration and Pseudomembrane

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

If any area cannot be assessed, circle one of the following:

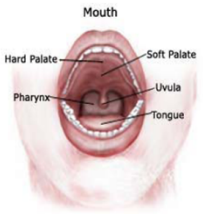
04 = Unable to visualize/assess due to severity
05 = Unable to assess because patient is sedated
06 = Unable to assess because patient is disoriented
07 = Unable to assess because patient is comatose
08 = Unable to assess because patient is unwilling or unable to cooperate
09 = Unable to assess because patient is not available. Explain: _____
_____
10 = Other. Explain: _____
99 = Missing

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

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

15.2 APPENDIX B: ORAL CGVHD CLINICAL SCORING INSTRUMENT

Mouth



Mucosal change	No evidence of cGVHD		Mild		Moderate		Severe	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate (≥25%) or Severe erythema (<25%)	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Hyperkeratotic changes(<25%)	1	Hyperkeratotic changes(25-50%)	2	Hyperkeratotic changes (>50%)	3
Ulcers	None	0	None	0	Ulcers involving (≤20%)	3	Severe ulcerations (>20%)	6
Mucoceles*	None	0	1-5 mucoceles	1	6-10 scattered mucoceles	2	Over 10 mucoceles	3
			*Mucoceles scored for lower labial and soft palate only				**Total score for all mucosal changes**	

15.3 APPENDIX C: NUMERIC RATING SCALES (0-10) FOR ORAL PAIN, SENSITIVITY, AND DRYNESS

ORAL PAIN

On a 0 to 10 scale, how PAINFUL is your mouth now? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No pain Worst pain

ORAL SENSITIVITY

On a 0 to 10 scale, how SENSITIVE is your mouth now? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No sensitivity Worst sensitivity

ORAL DRYNESS

On a 0 to 10 scale, how DRY is your mouth NOW? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No dryness Worst dryness

15.4 APPENDIX D: GLOBAL SCALE

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

Much worse	A little worse	Same	A little better	Much better

15.5 APPENDIX E: PAINOMETER (POM) ASSESSMENT SHEET

Baseline **Date: _____/_____/_____** **Time: _____** **Subject Study Number: _____**

I INSTRUCTIONS: Ask the participant to choose words from the Sensory pain intensity list and the Affective pain intensity list below to describe present oral pain- Circle the chosen letter/word and number/word from the lists.

SENSORY	AFFECTIVE
A Cramping	1. Nagging
B. Dull	2. Agonizing
C. Splitting	3. Annoying
D. Burning	4. Troublesome
E. Sore	5. Killing
F. Shooting	6. Tiring
G. Radiating	7. Unbearable
H. Hurting	8. Sickening
I. Crushing	9. Terrifying
J. Aching	10. Miserable
K. Stabbing	11. Torturing
L. Sharp	
M. Tearing	
N. Pressing	

II. INSTRUCTIONS: Ask the participant to choose the word which describes the duration of oral pain and check the response:

Continuous _____ Periodic (Comes and goes) _____

III. INSTRUCTIONS: Ask the participant to choose words from the Sensory pain intensity list and the Affective pain intensity list below to describe present oral pain with swallowing
Circle the letters/numbers and words chosen from the lists.

SENSORY	AFFECTIVE
A. Cramping	1. Nagging
B. Dull	2. Agonizing
C. Splitting	3. Annoying
D. Burning	4. Troublesome
E. Sore	5. Killing
F. Shooting	6. Tiring
G. Radiating	7. Unbearable
H. Hurting	8. Sickening
I. Crushing	9. Terrifying
J. Aching	10. Miserable
K. Stabbing	11. Torturing
L. Sharp	
M. Tearing	
N. Pressing	

IV. INSTRUCTIONS: Ask the participant to choose the word which describes the duration of oral pain with swallowing and (') the response

Continuous _____ Periodic (Comes and goes) _____

Scoring of Painometer (POM) Assessment Sheet

Weighted scores for the Painometer sensory word descriptors are:

A. Cramping = 4
B. Dull = 1
C. Splitting = 5
D. Burning = 4
E. Sore = 1
F. Shooting = 5
G. Radiating = 3
H. Hurting = 2
I. Crushing = 4
J. Aching = 3
K. Stabbing = 5
L. Sharp = 5
M. Tearing = 5
N. Pressing = 2

Weighted scores for the Painometer affective word descriptors are:

1. Nagging = 1
2. Agonizing = 4
3. Annoying = 1
4. Troublesome = 2
5. Killing = 5
6. Tiring = 3
7. Unbearable = 5
8. Sickening = 4
9. Terrifying = 5
10. Miserable = 3
11. Torturing = 5

Total score is calculated by simple summation of individual weighted scores.

15.6 APPENDIX F: ORAL HEALTH IMPACT PROFILE (OHIP-14) [38]

Date: ____/____/____ Timepoint: _____ LIP print name: Jacqueline Mays LIP Signature:_____

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

Total _____

15.7 APPENDIX G: SCHEDULE OF EVALUATIONS AND EVENTS

Patients Randomized to Clobetasol Oral Rinse Schedule:

Patient Evaluations and Events	**Screening and Baseline (Day -7 to 0)***	**Day 0 ***	**Interim Evaluation (Day 14) *g**	**End of Intervention (Day 28) ***	**Follow-up (Day 56) *** **(or end of treatment visit)**	**Follow up (3 months and 6 months post treatment)#**
History and Physical Exam[t]	X[t]		X[t]	X[t]	X[t]	X[t]
NIH Advanced Directives Form						
cGVHD NIH Organ Staging	X				X	
Clinical Photographs	X		X	X	X	
Urine pregnancy test	X					
Informed Consent	X					
Randomization	X					
CBC, Acute care, mineral and liver panel & LDH, TBNK	X		X	X	X	
Serum Cortisol Level	X		X	X	X	
Research Saliva and Plasma Collection	X		X	X	X	
OMRS	X		X	X	X	
Oral cGVHD Clinical Scoring	X		X	X	X	

Patient Evaluations and Events	**Screening and Baseline (Day -7 to 0)***	**Day 0 ***	**Interim Evaluation (Day 14) *g**	**End of Intervention (Day 28) ***	**Follow-up (Day 56) *** **(or end of treatment visit)**	**Follow up (3 months and 6 months post treatment)#**
Oral HSV by PCR	X			X		
Oral Pain, Sensitivity, Dryness Scales	X		X	X	X	
Global Scale			X	X	X	
POM	X		X	X	X	
OHIP-14 (Oral QOL)	X		X	X	X	
Biopsy/Tissue Collection	X			Xt		
ACTH Stimulation Test	X			X	Xp	
Adrenocorticotropic Hormone blood level	X			X	X	
Hemoglobin A1C level	X	X	X	X	X	
Compliance Evaluation			X	X		
Monitoring for Adverse Events			X	X	X	X
Start of intervention		X				
Completion of the intervention				X		

* ± 2 days

t Optional

[p] Per PI discretion (at day 56 or day 70 visit depending on subject randomization group) if there is concern for endocrine side-effects)

[#] This follow up can be done in person or via telephone call as per Section **3.7**[g] Patients initially randomized to 2 weeks of placebo will have two Day 14 Interim Evaluation visits, one at unblinding and one after 14 days of clobetasol therapy.

[h] As indicated in Section **11.5**, all subjects ≥ age 18 will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

15.8 APPENDIX H: DATA COLLECTION ELEMENTS REQUIRED BY PROTOCOL

All of the following elements will be recorded in the research database.

Patient Enrollment

Recipient

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

Donor

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

Study Drug administration and response for each course of therapy given

- Dates study rinse given
- Actual dose given
- Response assessment (OMRS score) for each visit

Laboratory and Diagnostic Test Data

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

Adverse Events

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

Concomitant Measures

- Baseline immunosuppressive medications
- Other therapy for recorded adverse events

Off study

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

15.9 APPENDIX I: TOPICAL CLOBETASOL 0.05% ORAL RINSE FOR ORAL CHRONIC GRAFT-VERSUS-HOST DISEASE PATIENT DIARY

INSTRUCTIONS: Rinse with the study medication THREE times a day for 2 minutes and spit out. Do not eat, drink or brush your teeth for at least 30 minutes after study medication use.

Rinse with the nystatin suspension ONE time a day for at least 30 seconds after your evening meal. Do not eat, drink or brush your teeth for at least 10 minutes after nystatin use.

You can use painkiller rinse (viscous lidocaine) as needed to relieve oral discomfort. Do not use the painkiller rinse at least 30 minutes before and after using the study rinse or nystatin. Do not use any other mouthwashes, rinses or oral hygiene products except toothpaste.

Record the level of oral pain and oral dryness for the day at its WORST using a number from 0 (no pain/dryness) to 10 (the worst possible pain/dryness).

Day of the week	Date	**Time** Write down the time you use a dose of study rinse and circle AM or PM. (Remember that you are to use the rinse 3 times per day)	**Mouth Pain Rating** Rate your pain with the first daily rinse by circling the number on the 0 to 10 pain scale. Zero (0) is no pain and ten (10) is the worst pain	**Mouth Dryness Rating** Rate your dryness before the first daily rinse by circling the number on the 0 to 10 pain scale. Zero (0) is no dryness and ten (10) is the worst dryness	**Medications for Pain** List any medications you have taken for **pain in your mouth** in the past 24hrs	**Side Effects** List any side effects that you have experienced in the past 24hrs	**Comments** Include any additional information such as why you missed/skipped a dose of study rinse
		Dose 1 AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2 AM/PM					
		Nystatin PM					
		Dose 3 AM/PM					
		Dose 1 AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2 AM/PM					
		Nystatin PM					
		Dose 3 AM/PM					
		Dose 1 AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2 AM/PM					
		Nystatin PM					
		Dose 3 AM/PM					
		Dose 1 AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2 AM/PM					
		Nystatin PM					
		Dose 3 AM/PM					
		Dose 1 AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2 AM/PM					
		Nystatin PM					
		Dose 3 AM/PM					
		Dose 1 AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2 AM/PM					
		Nystatin PM					
		Dose 3 AM/PM					
		Dose 1 AM/PM	0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10			
		Dose 2 AM/PM					
		Nystatin PM					
		Dose 3 AM/PM					

Patient Signature:________________________ Date:_________

15.10 APPENDIX J: SPANISH LANGUAGE TRANSLATIONS OF THE PATIENT-REPORTED OUTCOME FORMS

Painometer (POM) Assessment Sheet

Date: ____/____/____ Time: _____ Timepoint: _____ LIP: Jacqueline Mays LIP **Signature:**_____

I INSTRUCCIONES: Pídale al participante que elija palabras de la lista de intensidad del dolor Sensorial tanto como de la lista de intensidad de dolor Afectivo a continuación, para describir el dolor oral en estos momentos. Haga un círculo alrededor de la letra y palabra y del número y palabra de las listas a continuación.

SENSORIAL	AFECTIVO
A Calambre	1. Irritante
B. Leve	2. Agobiante
C. Enloquecedor	3. Fastidioso
D. Ardor	4. Molestoso
E. Adolorido	5. Mortal
F. Punzante	6. Fatigoso
G. Que irradia	7. Insoportable
H. Que duele	8. Deprimente
I. Triturante	9. Espantoso
J. Resentido	10. Miserable
K. Como puñaladas	11. Torturante
O. Agudo	
P. Desgarrante	
Q. Insistente	

II. INSTRUCCIONES: Pídale al participante que elija la palabra que describe la duración del dolor oral y marque la respuesta:

Continuo _____ Periódico (Se viene y se va) _

III. INSTRUCCIONES: Pídale al participante que elija palabras del listado de intensidad del dolor Sensorial y del dolor Afectivo a continuación, para describir el dolor oral al deglutir. Marque con un círculo las letras/números y los números/palabras de estas listas.

SENSORIAL	AFECTIVO
A Calambre	1. Irritante
B. Leve	2. Agobiante
C. Enloquecedor	3. Fastidioso
D. Ardor	4. Molestoso
E. Adolorido	5. Mortal
F. Punzante	6. Fatigoso
G. Que irradia	7. Insoportable

H. Que duele
I. Triturante
J. Resentido
K. Como puñaladas
L. Agudo
M. Desgarrante
N. Insistente
8. Deprimente
9. Espantoso
10. Miserable
11. Torturante

IV. INSTRUCCIONES: Pídale al participante que elija la palabra que describa la duración del dolor oral al deglutir y la respuesta.

Continuo _____ Periódico (Se viene y se va) _

Global Scale-0 to 10 Scales

Numeric Rating Scales (0-10) for Oral Pain, Sensitivity, and Dryness

DOLOR ORAL

En una escala del 0 al 10, ¿qué tanto DOLOR siente en su boca en este momento? Por favor marque el número adecuado con un círculo.

0 1 2 3 4 5 6 7 8 9 10

No siento dolor El peor que he sentido

SENSIBILIDAD ORAL

En una escala del 0 al 10, ¿qué tan SENSIBLE siente su boca en este momento? Por favor marque el número adecuado con un círculo.

0 1 2 3 4 5 6 7 8 9 10

No sufro de sensibilidad La peor sensibilidad que he sentido

RESEQUEDAD ORAL

En una escala del 0 al 10, ¿qué tan SECA siente su boca EN ESTE MOMENTO? Por favor marque el número adecuado con un círculo.

0 1 2 3 4 5 6 7 8 9 10

No siento resequedad La peor resequedad que he sentido

Escala Global

Si compara la condición actual de su boca, con la condición en la que estaba HACE DOS SEMANAS, ¿en que condición general esta su boca? Por favor, marque con un círculo.

Mucho peor Un poco peor Igual Un poco mejor Mucho mejor

LIP Print Name: Jacqueline Mays LIP Signature:_____

Date of Evaluation:_____

Timepoint:_____

15.11 APPENDIX K: ORAL HEALTH IMPACT PROFILE (OHIP-14)

Date: ____/____/____ Timepoint: _____ LIP print name: Jacqueline Mays LIP Signature:_____

#	**Ha tenido los siguientes problemas, debido a dificultades con su boca, sus dientes o dientes postizos:**	**Nunca (0)**	**Casi nunca (1)**	**Ocasional-mente (2)**	**Frecuente-mente (3)**	**Muy frecuen-te (4)**
1	¿Ha tenido dificultad al pronunciar palabras?					
2	¿Se ha empeorado el sentido del gusto ha empeorado?					
3	¿Ha estado adolorida su boca?					
4	¿Se siente incómodo al comer?					
5	¿Se siente muy consciente de sí mismo?					
6	¿Se siente tenso/a?					
7	¿Ha sido insatisfactoria su dieta?					
8	¿Ha tenido que interrumpir tiempos de comida?					
9	¿Se da cuenta que le es muy difícil relajarse?					
10	¿Se siente un poco avergonzado/a?					
11	¿Se ha sentido muy irritable hacia otras personas?					
12	¿Ha tenido dificultad haciendo cosas que usualmente ha hecho sin dificultad?					
13	¿Se siente menos satisfecho/a con su vida en términos generales?					
14	No ha podido funcionar del todo.					

Total _____

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English version translation of Appendix J

Painometer (POM) Assessment Sheet

Baseline **Date: ____/_____/_____** **Time: _____** **Subject Study Number: _____**

I INSTRUCTIONS: Ask the participant to choose words from the Sensory pain intensity list and the Affective pain intensity list below to describe present oral pain- Circle the chosen letter/word and number/word from the lists.

SENSORY	AFFECTIVE
A Cramping	1. Nagging
B. Dull	2. Agonizing
C. Splitting	3. Annoying
D. Burning	4. Troublesome
E. Sore	5. Killing
F. Shooting	6. Tiring
G. Radiating	7. Unbearable
H. Hurting	8. Sickening
I. Crushing	9. Terrifying
J. Aching	10. Miserable
K. Stabbing	11. Torturing
L. Sharp	
M. Tearing	
N. Pressing	

II. INSTRUCTIONS: Ask the participant to choose the word which describes the duration of oral pain and check the response:

Continuous _____ Periodic (Comes and goes) _____

III. INSTRUCTIONS: Ask the participant to choose words from the Sensory pain intensity list and the Affective pain intensity list below to describe present oral pain with swallowing
Circle the letters/numbers and words chosen from the lists.

SENSORY	AFFECTIVE
A. Cramping	1. Nagging
B. Dull	2. Agonizing
C. Splitting	3. Annoying
D. Burning	4. Troublesome
E. Sore	5. Killing
F. Shooting	6. Tiring
G. Radiating	7. Unbearable
H. Hurting	8. Sickening
I. Crushing	9. Terrifying
J. Aching	10. Miserable
K. Stabbing	11. Torturing
L. Sharp	

M. Tearing
N. Pressing

IV. INSTRUCTIONS: Ask the participant to choose the word which describes the duration of oral pain with swallowing and (') the response

Continuous _____ Periodic (Comes and goes) _____

Scoring of Painometer (POM) Assessment Sheet

Weighted scores for the Painometer sensory word descriptors are:

A. Cramping = 4
B. Dull = 1
C. Splitting = 5
D. Burning = 4
E. Sore = 1
F. Shooting = 5
G. Radiating = 3
H. Hurting = 2
I. Crushing = 4
J. Aching = 3
K. Stabbing = 5
L. Sharp = 5
M. Tearing = 5
N. Pressing = 2

Weighted scores for the Painometer affective word descriptors are:

1. Nagging = 1
2. Agonizing = 4
3. Annoying = 1
4. Troublesome = 2
5. Killing = 5
6. Tiring = 3
7. Unbearable = 5
8. Sickening = 4
9. Terrifying = 5
10. Miserable = 3
11. Torturing = 5

Total score is calculated by simple summation of individual weighted scores.

Numeric Rating Scales (0-10) for Oral Pain, Sensitivity, and Dryness

ORAL PAIN

On a 0 to 10 scale, how PAINFUL is your mouth now? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No pain Worst pain

ORAL SENSITIVITY

On a 0 to 10 scale, how SENSITIVE is your mouth now? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No sensitivity Worst sensitivity

ORAL DRYNESS

On a 0 to 10 scale, how DRY is your mouth NOW? Please circle the number.

0 1 2 3 4 5 6 7 8 9 10

No dryness Worst dryness

Global Scale

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

Much worse A little worse Same A little better Much better

Oral Health Impact Profile (OHIP-14) [38]

Date: ____/____/____ Timepoint: _____ LIP print name: Jacqueline Mays LIP Signature:_____

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

Total _____