DEXAMETHASONE SOLUTION AND DEXAMETHASONE IN MUCOLOX™ FOR THE TREATMENT OF ORAL INFLAMMATORY ULCERATIVE DISEASES

PROTOCOL: NCT04540133

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LIST OF ABBREVIATIONS

AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
cGVHD	chronic graft versus host disease
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
OLP	Oral lichen planus
PI	Principal Investigator
SAE	serious adverse experience

PROTOCOL SYNOPSIS

TITLE	**DEXAMETHASONE SOLUTION AND DEXAMETHASONE IN MUCOLOX™ FOR THE TREATMENT OF ORAL INFLAMMATORY ULCERATIVE DISEASES**
SPONSOR	Professional Compounding Centers of America
FUNDING ORGANIZATION	
NUMBER OF SITES	1
RATIONALE	Topical steroid therapy is considered the first line of treatment for Oral Inflammatory Ulcerative Diseases with current treatment regimens requiring multiple application or rinses daily. Although topical steroid therapy can be successful for most patients, the treatment schedule can be challenging to maintain. There is therefore considerable interest in developing new and more effective therapies that require less frequent applications. The possibility of having a treatment agent that is safe, easy to use, and cost effective, with potentially greater efficacy than the current standard of care available topical steroid solutions would be ideal. Using Mucolox™ as a vehicle to deliver topical dexamethasone to the oral mucosa has the potential to effectively prolong contact time between the medication and mucosa, leading to improved clinical outcomes due to the need for less frequent application. This technology would help to more efficiently achieve high drug concentrations locally. By possibly shortening the frequency and time of topical therapy and improving patient compliance, this may translate to greater therapeutic benefit.
STUDY DESIGN	This is a randomized, phase 2 study.
PRIMARY OBJECTIVE	The primary objective of this study is to determine the clinical efficacy and tolerability of compound dexamethasone at 0.5 mg/5 mL in Mucolox™ for the treatment of Oral Inflammatory Ulcerative Diseases as measured by a reduction in oral symptoms between patients treated with compounded dexamethasone 0.5mg/5ml solution in Mucolox™ (group A) and patients treated with topical commercial dexamethasone 0.5mg/5ml solution only (group B).
SECONDARY OBJECTIVES	The secondary objectives are: • To determine the clinical improvement in clinician-reported outcome measures achieved by treatment with topical compounded dexamethasone at 0.5 mg/5 mL in Mucolox™ compared to commercial dexamethasone 0.5mg/5ml solution alone. • To assess the tolerability of Oral Inflammatory Ulcerative Diseases as measured with the 14-item Oral Health Impact Profile (OHIP-14).
NUMBER OF SUBJECTS	30
SUBJECT SELECTION	Inclusion Criteria:

CRITERIA	Age 18 years and older. Patients with symptomatic biopsy proven Oral Inflammatory Ulcerative Diseases (worst VAS sensitivity score ≥ 7 over the last week). Ability to understand and the willingness to sign a written informed consent document. <u>Exclusion Criteria:</u> Patients already on topical or systemic steroids. Inability to comply with study instructions. Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements. VAS sensitivity score < 7. Pregnant women. A urine pregnancy test will be performed for women of child bearing potential. Allergy to fluconazole Patients on medications that have a strong interaction with fluconazole Patients with advanced liver disease
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Dexamethasone 0.5 mg/5mL in Mucolox compounded oral solution swish and spit TID for 4 weeks
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Dexamethasone 0.5 mg/5mL (NDC 00054-3177-63; Roxane Laboratories, Columbus, OH 43216-6532) oral solution swish and spit TID for 4 weeks
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 28 days **Screening:** day 0 **Treatment:** 28 days **Follow-up:** Day 28 ± 5 days The total duration of the study is expected to be 4 weeks.

CONCOMMITANT MEDICATIONS	Allowed: all Prohibited: none
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• Change from pre to post treatment in each subject's subjective sensitivity score (0-10) evaluated at baseline and 4 weeks post treatment for each arm. We will also compare changes of the daily subject's subjective sensitivity score (0-10) over time for each arm.
SECONDARY ENDPOINTS	• The secondary endpoints include the evaluation of objective data using the REU scoring system and the oral health related quality of life using the OHIP-14.
OTHER EVALUATIONS	*None*
SAFETY EVALUATIONS	The safety of participants and the overall study will be monitored continuously throughout the study period. At the 4 week visit, evaluating doctors will review the participants' diaries for self-reported adverse events.
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed the study, an interim analysis for safety will be conducted by an independent data monitoring committee. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	Pre-to-post treatment improvement will be assessed using McNemar's test within each arm. The REU scores will be summarized descriptively for each arm at pre-treatment, post-treatment, and pre-to-post treatment change. The pre-to-post treatment change will be compared between the arms using either student's t-test or Mann–Whitney test, depending on the distribution of the data.
Rationale for Number of Subjects	The sample size was calculated to ensure at least 80% power and two-sided alpha of 0.05 in detecting a t difference of 2.0 points oral pain on an 11 point scale (VAS 0-10) between Arm A and B.

1 BACKGROUND

Oral Inflammatory Ulcerative Diseases are relatively common conditions seen in oral medicine practices. These include oral lichen planus (OLP), pemphigus vulgaris, mucous membrane pemphigoid (MMP) and oral chronic graft versus host disease (cGVHD).

Oral lichen planus

Oral lichen planus (OLP) is a benign, chronic condition that occurs in 1 to 2% of adults[1]. Middle-aged women are twice as likely to be affected as men. OLP may be associated with a variety of systemic and local conditions and medication use such as thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, beta blockers, gold salts, sulfasalazine, sulfonylureas and penicillamine. Biologic agents such as tumor necrosis factor (TNF) alpha inhibitors may also cause lichen planus-like eruptions[2]. Amalgam and composite restorations may cause localized contact lichenoid hypersensitivity reactions possibly to mercury and formaldehyde.

OLP can affect any mucosal surface, and most commonly affects the buccal mucosa and tongue bilaterally. OLP can present with three distinct forms: reticular/keratotic, erosive/erythematous, and ulcerative forms. The reticular/keratotic form, characterized by Wickham striae, is the most common form and is often asymptomatic. Occasionally patients will report discomfort and describe the buccal mucosa as “rough,” “thick,” or “tight”. The erosive/erythematous form typically presents as desquamative gingivitis. Patients may complain of discomfort while eating acidic, spicy or crunchy food. The ulcerative form is the most severe and presents as shallow ulcerations that have a yellow fibrin membrane on the surface. Often, there is a combination of the three forms at different sites, or at different times. Most patients exhibit a characteristic bilateral and symmetric distribution of lesions, typically involving the buccal mucosa, dorsum and ventral surfaces of the tongue and/or gingiva.

The diagnosis of oral lichen planus is based primarily on clinical characteristics, although biopsy may be indicated when the presentation is not typical (e.g. unilateral presentation, or lack of reticulation features)[3,4]. Histopathological examination demonstrates a lymphocytic band of variable thickness at the interface and degeneration or loss of the basal cell layer.

Mucous membrane pemphigoid

Mucous membrane pemphigoid is an autoimmune vesiculobullous disease associated with increased frequency of HLA-DQB1*0301 and characterized by autoreactive antibodies, usually IgG and sometimes IgA that target antigens in the epithelium-attachment complex resulting in subepithelial blistering and mucosal fragility [5]. MMP may involve the larynx, nose, eyes, and genital mucosa. One of the major complications is conjunctival scarring that can lead to blindness (hence the older term “cicatricial pemphigoid”). Scarring may also involve the larynx and esophagus, but fortunately is uncommon in the oral mucosa.

The oral mucosal lesions almost always affect the gingiva leading to bright red or “desquamative gingivitis”. This is caused by epithelium peeling off the gingiva leaving only exposed connective tissue which is the basis for a positive Nikolsky sign. Ulcers may develop on the gingiva and elsewhere in the mouth such as the palatal, buccal and tongue mucosa. Biopsy of a perilesional area for histopathological examination and direct immunofluorescence (DIF) studies is essential for a definitive diagnosis; DIF shows deposition of IgG, C3 and sometimes IgA at the basement membrane zone.

Management includes topical treatment with corticosteroids or tacrolimus. Systemic agents such as prednisone, dapsone, azathioprine, tetracycline, nicotinamide and cyclophosphamide may be

required for management of refractory oral MMP. When the skin is involved, the diagnosis is bullous pemphigoid.

Pemphigus vulgaris
Pemphigus vulgaris (PV) is an uncommon autoimmune vesiculo-bullous disorder that affects mainly older adults and was fatal in the pre-steroid era. PV has a predilection for Ashkenazi Jews (who exhibit a high frequency of HLA-B38 or HLA-B35), Arabs and others individuals from the Mediterranean region. Different HLA subtypes are implicated in PV in Caucasians and Asians. Autoantibodies, mostly IgG are directed towards the inter-epithelial cementing substance, leading to intra-epithelial blistering [6]. Oral ulcers, present in 95% of patients, are often the first sign of PV with skin lesions developing later. Oral lesions are characterized by painful, irregular, erythematous depressed erosions with whitish tissue tags at the edges; yellow ulcerations may also be present. The most common affected oral sites are the hard and soft palatal mucosa (likely because of physiologic trauma from swallowing), gingiva (also presenting as "desquamative gingivitis"), buccal mucosa and tongue. Diagnosis is established through a perilesional tissue biopsy for histopathologic evaluation and DIF which shows intercellular deposition of IgG.

Topical corticosteroid therapy or topical tacrolimus are the mainstays of therapy. More severe or refractory cases require systemic agents such as prednisone, mycophenolate mofetil, azathioprine and cyclosporine. For severe cases and if the skin is involved, specialist referral is indicated and treatment is generally with prednisone, rituximab (a monoclonal antibody), IVIg, or extracorporeal photopheresis.

Chronic graft-versus-host disease
Chronic graft-versus-host disease remains a significant complication of allogeneic hematopoietic cell (bone marrow) transplantation and continues to be the leading cause of non-relapse mortality. The oral cavity is affected in around 80% of cases. [7] The spectrum of oral manifestations in cGVHD includes reticular white lichen planus-like changes with erythema and minimal ulceration that affects both the keratinized and non-keratinized mucosa. Patients typically complain of sensitivity to spicy, acidic food or strongly flavored products. Topical therapy is similar to that for OLP. Based on the NIH ancillary therapy and supportive care guidelines, initial therapy for most patients is with dexamethasone solution 0.5mg/5mL; patients are instructed to swish/gargle for 4-6 minutes then spit, 4-6 times per day and to avoid eating or drinking for 10-15 minutes using the medication. Other topical steroids with higher potency may also be prescribed (e.g., clobetasol).

1.1 Overview of Clinical Studies

1.1.1 Management of Oral Inflammatory Ulcerative Diseases

Available therapies for Oral Inflammatory Ulcerative Diseases are aimed at managing symptoms through the reduction of inflammation. The mainstay of therapy remains use of topical corticosteroids which can be delivered in various vehicles including gels and solutions[1,8,9]. A response to treatment with midpotency corticosteroids (e.g., triamcinolone acetonide 0.1%), potent fluorinated corticosteroids (e.g., fluocinolone acetonide 0.1% and fluocinonide 0.05%), and super-potent halogenated corticosteroids (e.g., clobetasol propionate 0.05%), has been reported in 30–100% of treated individuals[10-15].

One of the challenges in applying topical corticosteroids is the lack of adherence to the oral mucosa for an adequate duration for the medication to be locally absorbed. Numerous obstacles are encountered when a topical steroid is prescribed to treat Oral Inflammatory Ulcerative

Diseases, including the presence of saliva, changes in taste, poor tissue penetration, enzymatic degradation, and the need for frequent dosing, all of which may negatively affect patient compliance[16]. One approach to develop more efficacious and safer therapies could be inflammation-targeting drug delivery to achieve high drug concentrations locally at the site of inflammation with minimal exposure of healthy or distant tissues.

Use of topical steroids for Oral Inflammatory Ulcerative Diseases may lead to the development of secondary candidiasis in 11-47% of patients, which requires antifungal therapy[13,17,18]. Fluconazole 200 mg once weekly has been showed to be an effective prophylaxis measure to prevent oral candidiasis infection[19-21]. Although there are some reports of systemic absorption and adrenal suppression from super-potent topical steroids in the treatment of chronic dermatologic disorders, adrenal suppression is uncommon even in long-term oral application of topical corticosteroids such as fluocinonide and clobetasol[22-24]. Systemic absorption from topical steroids has been reported and it is thought that absorption of small amounts through the oral mucosa can take place, but clinical experience and laboratory studies have shown this not to be of clinical significance in almost all cases[25]. Gonzalez-Moles et al. reported two cases of moon facies (2/30) and two cases of hirsutism (2/30) secondary to long-term use (> 4 weeks) of clobetasol 0.05% solution for the treatment of oral erosive lesions. All cases resolved upon discontinuation of the medication and/or reduction in frequency of administration. Other side effects reported include nausea, mucosal atrophy, xerostomia, halitosis and delayed healing[25,26].

1.1.2 Dexamethasone solution for Oral Inflammatory Ulcerative Diseases

The efficacy of dexamethasone solution has been well described in several clinical trials. Rhodus et al. conducted a prospective controlled clinical trial to test the efficacy of dexamethasone solution in 13 patients with oral erosive-ulcerative lichen planus[27]. Patients were instructed to rinse with 5 ml of dexamethasone 0.1% solution for 3 min and then to expectorate. Subjective symptomatology (pain and/or discomfort) was recorded on a 100 mm visual analogue scale (VAS) at first visit and at 6 week follow up. Patients experienced significant subjective improvement in symptoms following the dexamethasone treatment (VAS score pre-treatment: 6.7 ± 1.4; VAS score post-treatment: 2.3 ± 0.6).

Hambly et al. conducted a single-blinded, cross-over pilot trial in nine patients to compare the efficacy of compounded dexamethasone solution for OLP[28]. Patients were instructed to rinse with 2 ml of dexamethasone 0.5 mg/2 mL compounded as a solution or one 0.5 mg tablet crushed and mixed with 20 ml water three times per day for 3 weeks. All patients were instructed to rinse and hold the medication in their mouths for at least 2–3 minutes and then expectorate. Participants were evaluated at weeks 0, 3, 4, and 7. Symptoms were recorded with a 100-mm VAS; other assessments included the Treatment Satisfaction Questionnaire for Medication-9, comparisons of clinical photographs, and self-assessment via patient daily diary (Appendix 2) entries to record compliance with each dose. Results showed the compounded dexamethasone solution to be more effective compared to 0.5 mg dexamethasone tablet crushed and mixed with 20 ml water in terms of compliance, patient-perceived faster onset of action, and improved symptom relief.

1.1.3 Mucolox™

Mucolox™ is a mucoadhesive polymer gel that can be used in pharmaceutical compounding for the management of diseases and conditions of the oral mucosa including oral mucositis, and mouth ulcers[29,30]. The safety and toxicological profile of Mucolox™ was evaluated in vitro and compared to Triton X- 100 (positive control) and distilled water (negative control), using a 3-

dimensional model of the human oral mucosa. Results showed that Mucolox™ can bind to tissues six times longer than Triton X-100 (before 50% cell viability) therefore offering increased retention of medication at the site of action. Additionally, at 4.5 hours, the difference in percent cell viability between Mucolox™ and distilled water was not significant, making it a safe water-soluble mucosal delivery system.

A recent study from our group showed that commercial dexamethasone 0.5mg/5mL solution compounded with Mucolox™ was found to be a safe option for the management of oral lichen planus when rinsed three times a day for 5-minute swish and expectorate[31]. Subjects receiving dexamethasone 0.5mg/5mL solution in Mucolox™ had a better clinical response compared to dexamethasone 0.5mg/5mL commercial solution alone (6-point reduction vs. 4.3; $p<0.001$) of reticulation/keratosis, erythema, and ulceration (REU) scores. Both arms had a subjective improvement of the oral symptoms after 4 weeks of treatment.

2 STUDY RATIONALE

There is a significant unmet need for optimized topical therapies for Oral Inflammatory Ulcerative Diseases. Topical steroid therapy is considered the first line of treatment for Oral Inflammatory Ulcerative Diseases with current treatment regimens requiring multiple application or rinses daily[27,32,33]. Although topical steroid therapy can be successful for most patients, the treatment schedule can be challenging to maintain. There is therefore considerable interest in developing new and more effective therapies that require less frequent applications. The possibility of having a treatment agent that is safe, easy to use, and cost effective, with potentially greater efficacy than the current standard of care available topical steroid solutions would be ideal. Using Mucolox™ as a vehicle to deliver topical dexamethasone to the oral mucosa has the potential to effectively prolong contact time between the medication and mucosa, leading to improved clinical outcomes due to the need for less frequent application. This technology would help to more efficiently achieve high drug concentrations locally. By possibly shortening the frequency and time of topical therapy and improving patient compliance, this may translate to greater therapeutic benefit. Our initial work in a small number of oral lichen planus patients has demonstrated the efficacy of dexamethasone 0.5mg/5mL solution in Mucolox™ in significantly improving signs and symptoms of OLP compared to dexamethasone 0.5mg/5mL solution only[31]. As such, dexamethasone 0.5mg/5mL solution in Mucolox™ has the potential to be used also for other Oral Inflammatory Ulcerative Diseases.

2.1 Risk / Benefit Assessment

2.1.1 Drug side effects and toxicities

Potential side effects with dexamethasone 0.5mg/5mL solution used as an oral topical rinse include an increased risk of developing oropharyngeal candidiasis and systemic absorption. All patients will be prescribed antifungal prophylaxis while on study with fluconazole 200 mg once a week. All participants will be informed that they may withdraw from the study at any time. As a topically applied agent, dexamethasone therapy can be discontinued at any time without any complications. Any noted clinical response will be expected to be reversed in such situations.

Prolonged application of potent topical corticosteroids (e.g., > 50 g of clobetasol propionate or > 500 g of hydrocortisone per week) may lead to short-term hypothalamic-pituitary-adrenal axis alteration. In our study, in case of any systemic absorption, the maximum dose would be 10.5 mg/week (5 mL x 0.1 mg/mL = 0.5 mg/rinse, 3 times/day = 1.5 mg, 7 days/week = 10.5 g). We do not expect there to be significant systemic absorption, and therefore do not expect systemic side

effects of dexamethasone solution when used as a swish and spit. Mucolox™ is a vehicle for drug delivery used in compounding medications with ingredients expected to be harmless. No major side effects from dexamethasone 0.5mg/5mL solution and dexamethasone 0.5mg/5mL solution in Mucolox™ use were reported in our first preliminary study[31].

2.1.2 Potential benefits for participating individuals

All subjects will be assigned an active treatment. Thus, it is anticipated that the majority of participants may benefit from participation in this study. Additionally, most participants may benefit from the satisfaction in knowing that their involvement has a potential impact on the clinical care of future patients suffering from their condition.

3 STUDY OBJECTIVES

3.1 Primary Objective

The objective of this single center, 4-week, open label randomized, phase II study is to determine the clinical efficacy and tolerability of compound dexamethasone at 0.5 mg/5mL in Mucolox™ for the treatment of Oral Inflammatory Ulcerative Diseases as measured by a reduction in oral symptoms between patients treated with compounded dexamethasone 0.5mg/5ml solution in Mucolox™ (group A) and patients treated with commercial topical dexamethasone 0.5mg/5ml solution only (group B).

Completion of this study will establish important data on the efficacy of topical steroid therapy when combined with a carrier and delivery system such as Mucolox™.

3.2 Secondary Objectives

The secondary objectives are:

- To determine the clinical improvement in clinician-reported outcome measures achieved by treatment with topical compounded dexamethasone at 0.5 mg/5 mL in Mucolox™ compared to commercial dexamethasone 0.5mg/5ml solution alone.
- To assess the tolerability of Oral Inflammatory Ulcerative Diseases as measured with the 14-item Oral Health Impact Profile (OHIP-14).

4 STUDY DESIGN

4.1 Study Overview

This is a single center, 4-week, open label randomized, phase II study. Randomization will be conducted by the UCSF Investigational Drugs Services (IDS) Pharmacy. The study period will be four weeks, which based on previous studies should be an adequate period to assess significant clinical improvement. Subjects will be evaluated clinically at baseline before starting treatment and at the end of the four-week period, for a total of two visits. Subjects will be randomized to either compounded dexamethasone in Mucolox™ or commercial dexamethasone solution only. Subjects will return for evaluation after four weeks at which time the primary end-points will be assessed. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

Experimental treatment: Dexamethasone solution (0.5mg/5ml) in Mucolox™

Comparator: Commercial Dexamethasone solution (0.5mg/5ml)

Total duration of subject participation will be four weeks. Total duration of the study is expected to be 4-5 weeks.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary endpoint will be a change from pre to post treatment in each subject's subjective sensitivity score (0-10) evaluated at baseline and 4 weeks post treatment for each arm. We will also compare changes of the daily subject's subjective sensitivity score (0-10) over time for each arm.

5.2 Secondary Efficacy Endpoints

The secondary objectives include the evaluation of objective data using the REU scoring system and the oral health related quality of life using the OHIP-14. For the analysis of secondary endpoints see the statistical section.

5.3 Safety Evaluations

The safety of participants and the overall study will be monitored continuously throughout the study period. At the 4 week visit, evaluating physicians will review the participants' diaries for self-reported adverse events. Subjects will be instructed to contact their treating physician by phone or email to report any unexpected side effects or side effects lasting more than 7 days, should they occur. Any necessary medical intervention will be handled by the treating physician. Data accuracy and protocol compliance will be monitored and assured by the Principal Investigator and toxicities will be reported promptly to the IRB

6 SUBJECT SELECTION

6.1 Study Population

The Sol Silverman Oral Medicine Clinic is a major referral center for oral medicine patients including patients with Oral Inflammatory Ulcerative Diseases. Clinical diagnosis of Oral Inflammatory Ulcerative Diseases will be made by the patient's oral medicine specialist. Patients with a confirmed clinical diagnosis of Oral Inflammatory Ulcerative Diseases and with oral symptoms (defined as the worst VAS sensitivity score ≥7 over the last week) will be eligible **for participation in this study.** Potentially eligible subjects will be screened by one of the investigators by asking patients to rate their worst oral pain score (0-10) over the previous week. Those answering with at least a score of "7" (1/10) and that meet all other eligibility requirements (see below) will be eligible for enrollment. All patients (and/or parents/guardians) will sign informed consent for participation. All patients will be offered the opportunity to take home the consent form, and call back if they wish to participate.

6.2 Inclusion Criteria

1. Male or female ≥ 18 years of age at Visit 1.

2. Patients with symptomatic (worst VAS sensitivity score ≥ 7 over the last week) Oral Inflammatory Ulcerative Diseases
3. Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Patients already on topical or systemic steroids.
2. Inability to comply with study instructions.
3. Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.
4. VAS sensitivity score < 7.
5. Pregnant women. A urine pregnancy test will be performed for women of child bearing potential.
6. Allergy to fluconazole
7. Allergy to dexamethasone or other steroids
8. Patients on medications that have a strong interaction with fluconazole
9. Patients with advanced liver disease
10. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

7 CONCURRENT MEDICATIONS

There will be no restrictions on concomitant medications or supportive care measures.

All subjects will be treated with fluconazole 200 mg tablets once-a-week dosing for prophylaxis as topical steroid therapy may increase the risk of candidiasis. This is typically very effective at preventing candidiasis in susceptible patients, and since there are no interim clinical visits, this will minimize the risk of secondary infection, which if not detected early, could confound the results at the week 4 evaluation. A single weekly dose of fluconazole is not sufficient to have an impact on therapeutic levels of other medications. Fluconazole is a pregnancy category D drug. A such, pregnant women will be excluded from this study.

Any subjects that are already taking a systemic antifungal medication at the time of study enrollment will continue their prescribed medication and will not need to take the additional weekly fluconazole dose.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Randomization will be predetermined by a computer-generated list and coordinated by the UCSF Investigational Drugs Services Pharmacy. Patients will be assigned to one of two groups: 1) Arm A: compounded dexamethasone 0.5mg/5ml solution in Mucolox™ or 2) commercial dexamethasone 0.5mg/5ml solution only (ARM B).

8.2 Blinding

This is an open label trial with no blinding.

8.3 Formulation of Test and Control Products

8.3.1 Mucolox™

Description

Mucolox™ (PCCA, Houston, TX 77099) is a mucoadhesive polymer designed to improve mucoadhesion and prolong retention of medications at application sites within the oral mucosa. The composition of Mucolox™ is outlined in the table below.

Ingredient Name	INCI Name/Technical Name	Classification	FDA Reference
Potassium Sorbate NF	Potassium Sorbate	Subpart D – Chemical Preservatives	21 CFR 582.3640
Sodium Benzoate NF	Sodium Benzoate	Subpart D – Chemical Preservatives	21 CFR 582.3733
Glycerin USP (Natural)	Glycerin	Subpart B – General Purpose Food Additive	21 CFR 582.1320
Edetate Disodium USP Dihydrate	Disodium EDTA	FDA has no questions regarding intended use.	GRN000363
Pullulan	Pullulan	FDA has no questions regarding intended use in certain foods.	GRN000099
Tamarindus Indica Seed Polysaccharide	Tamarindus Indica Seed Polysaccharide	FDA has no questions regarding intended use.	GRN000503
Isomalt	Isomalt	Self-Determined GRAS (1996)	GRN6G0321
Simethicone USP	Simethicone	Used in Various Routes, Dosage Forms and Maximum Potencies	UNII: Multiple (Mixture)
Sodium Hyaluronate	Sodium Hyaluronate	Used in Various Routes, Dosage Forms and Maximum Potencies	UNII: YSE9PPT4TH
Poloxamer 407	Poloxamer 407	Used in Various Routes, Dosage Forms and Maximum Potencies	UNII: TUF2IVW3M2
Zea Mays (Corn) Starch	Zea Mays (Corn) Starch	Used in Various Routes, Dosage Forms and Maximum Potencies	UNII: O8232NY3SJ
Carbomer	Carbomer	Used in Various Routes, Dosage Forms and Maximum Potencies (Type: Proprietary)	UNII: Type Proprietary
Water	Water	N/A	UNII: 059QF0KO0R

Compatibility

N/A

Handling

There are no special handling requirements.

Availability

Compounded dexamethasone solution in Mucolox™ will be dosed at a concentration of 0.5 mg/5mL and dispensed through the UCSF Investigational Drugs Services Pharmacy. The prescription for the patients in ARM B (dexamethasone) will also be dispensed through the UCSF Investigational Drugs Services Pharmacy.

Preparation

Study subjects will be given a kit with the following, including detailed written instructions (see Appendix 1):

ARM A

- A four week supply of compounded dexamethasone solution in Mucolox™ will be dispensed, with extra for error and spillage, which will be rounded to 480 mL bottle at a concentration of 0.5 mg/5mL.
- Small dosing cups

Administration

Subjects will be instructed to rinse with 5 ml of compounded dexamethasone solution in Mucolox™ (0.5 mg/5ml; ARM A) for 5 minutes. After 5 minutes, subjects will be instructed to expectorate and to not eat or drink for 15 minutes after. The rinses will be completed three times per day, equally spaced during awake hours. If a study rinse is missed, subjects will be asked to attempt to make up for the missed rinse later the same day, to maintain four rinses per day. If necessary, for example, two consecutive 5-minute rinses can be completed at night before bed. This does not pose any known safety risk.

Ordering

Study rinses will be ordered through the UCSF Investigational Drugs Services Pharmacy.

Availability

Dexamethasone 0.5mg/5mL solution in Mucolox will be compounded and dispensed through the UCSF Investigational Drugs Services Pharmacy.

Destruction and Return

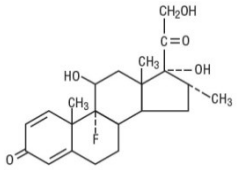
Patients should not continue to use any unused study supply once they have completed the study. It should be returned to the investigator and will be sent to pharmacy for destruction.

8.4 Dexamethasone solution

Description

Dexamethasone (NDC 00054-3177-63; Roxane Laboratories, Columbus, OH 43216-6532) is a synthetic adrenocortical steroid commercially available as a 0.5mg/5mL solution. It is stable in air and practically insoluble in water.

- The molecular weight is 392.47.
- The molecular formula is $C_{22}H_{29}FO_5$
- The structural formula is:



Each 5 mL of oral solution contains 0.5 mg of dexamethasone and citric acid, disodium edetate, flavoring, glycerin, methylparaben, propylene glycol, propylparaben, sorbitol and water.

Storage and Stability

Dexamethasone solution is stable at room temperature for 30 days after opening per package insert.

Compatibility

N/A

Handling

There are no special handling requirements.

Availability

Dexamethasone 0.5mg/5mL solution will be dispensed through the UCSF Investigational Drugs Services Pharmacy.

Preparation

Study subjects will be given a kit with the following, including detailed written instructions (see Appendix 1):

ARM B

- A four-week supply of dexamethasone solution will be dispensed, with extra for error and spillage, which will be rounded to 480 mL bottle at a concentration of 0.5 mg/5mL.
- Small dosing cups

Administration

Subjects will be instructed to rinse with 5 ml of the prescribed dexamethasone 0.5mg/5ml solution (ARM B) for 5 minutes. After 5 minutes, subjects will be instructed to expectorate and to not eat or drink for 15 minutes after. The rinses will be completed three times per day, equally spaced during awake hours. If a study rinse is missed, subjects will be asked to attempt to make up for the missed rinse later the same day, to maintain four rinses per day. If necessary, for example, two consecutive 5 minute rinses can be completed at night before bed. This does not pose any known safety risk.

Ordering

Dexamethasone solution will be ordered through the UCSF Investigational Drugs Services Pharmacy.

Destruction and Return

Patients should not continue to use any unused study supply once they have completed the study. It should be returned to the investigator for destruction.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.6 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary (Appendix 2) noting the day and date they take their study drug and any adverse events. They will be asked to bring their patient diary to each study visit along with all used and unused study drug containers.

9 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Study Visits 1, and at early termination when applicable. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.2 Study procedures

Potentially eligible subjects will be screened by one of the investigators by asking patients to rate their worst oral pain or pain score (0-10) over the previous week on a VAS. Those answering with at least a score of "7" (1/10) and that meet all other eligibility requirements (see Section 6) will be eligible for enrollment. All patients will sign informed consent for study participation. Each study visit is anticipated to take approximately 45 minutes. A urine pregnancy test will be performed for women of child bearing potential.

There is no financial compensation for participating in this study. Treatment will be administered on an outpatient basis. Study medication will be prescribed by authorized study staff physicians and filled by the Investigational Pharmacy at no expense for the patient. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's Oral Inflammatory Ulcerative Diseases.

Subjects will be evaluated clinically at baseline before starting treatment and at the end of the four-week period, for a total of two visits. Comprehensive subjective and objective data will be collected (Appendix 3 & 4) and intraoral photographs will be obtained. Oral mucosal disease will be evaluated using both patient reported (questions/visual analog scales) and clinician assessed measures.

Subjects will be prescribed compounded dexamethasone 0.5mg/5ml solution in Mucolox™ (ARM A) or commercial dexamethasone 0.5mg/5ml solution only (ARM B). All subjects will also receive a prescription for fluconazole 200 mg tablets once-a-week as prophylactic antifungal therapy. Any subjects that are already taking an antifungal oral medication at the time of the study enrollment will continue their prescribed medication and will not need to take the additional weekly fluconazole dose. Subjects will return for evaluation after four weeks at which time the study endpoints will be assessed.

If there is worsening of Oral Inflammatory Ulcerative Diseases that requires initiation of new immunomodulatory medications (systemic or topical), patients will remain on treatment, but will be regarded as unevaluable for the primary endpoint.

	Day 1 (baseline)	Day 28 ± 5 days (end of study)
Clinical examination	x	x
OHIP-14	x	x
Patient Reported Outcomes	x	x

9.2.1 Clinician Reported Outcomes

Mucosal disease will be measured using the REU scoring system for monitoring Oral Inflammatory Ulcerative Diseases[34]. Assessment requires only a light source and a dental mirror. This is a validated semiquantitative instrument for monitoring reticular/hyperkeratotic, erosive/erythematous, and ulcerative OLP lesions. The oral cavity is divided into ten sites: right buccal mucosa, left buccal mucosa, tongue dorsum, tongue ventrum, maxillary gingiva, mandibular gingiva, floor of mouth, hard palatal mucosa, soft palate and tonsil, and labial mucosa (upper and lower together). The severity of each type of lesion is scored according to the presence or absence of reticulations/hyperkeratosis (0 = absent; 1 = present), and the size of the erosions/erythema or ulcers (in cm^2) (0 = no involvement; 1-3 in increasing area of involvement). Because each type of lesion causes different degrees of discomfort and pain, each type of lesion is weighted accordingly: reticular lesions are weighted 1 because this presentation tends to be asymptomatic; erosive/erythematous lesions are weighted 1.5 since they tend to cause some degree of discomfort; ulcerative lesions are weighted 2.0 since they tend to be the most painful. The scores for each anatomic site are then totaled.

Intraoral photographs will be obtained at each visit.

9.2.2 Oral Health Impact Profile

Patients will complete the 14-item Oral Health Impact Profile (OHIP-14) instrument at baseline and at the end of treatment[35]. This is a validated instrument that assesses various aspects of oral health and function that has been shown to perform well in patients with oral mucosal diseases, including Oral Inflammatory Ulcerative Diseases[36].

9.2.3 Patient Reported Outcomes

Subjective assessments of subjects' oral symptoms will be obtained by using instruments from the NIH consensus documents for oral cGVHD, a condition that is very similar to other Oral Inflammatory Ulcerative Diseases (see Appendix 3 &4). These include report of mouth sensitivity at rest and sensitivity with stimulation (e.g. eating) on an eleven point scale. For the primary endpoint the worst sensitivity in the past week will be used. The clinician seeing the subject will

complete these forms at each study visit. Patients will also report daily sensitivity on an eleven point scale (see Appendix 2). Tolerability and compliance will also be evaluated, and a patient reported global assessment of overall improvement will be evaluated at the four-week visit.

9.2.4 Treatment Regimen

A four week supply of compounded dexamethasone 0.5mg/5ml solution in Mucolox™ (Arm A) and dexamethasone 0.5mg/5ml solution (Arm B) will be dispensed. The treatment instructions will be to rinse and spit (NOT swallow) with one teaspoon (5 mL) of solution, three times a day for 5 minutes at a time, and not to eat or drink for 15 minutes afterwards. Subjects will maintain a diary (Appendix 2) and record each dose, the length of time rinsing, and any adverse effects (e.g. transient burning).

Regimen Description						
	Agent	**Premedications; Precautions***	**Dose**	**Route**	**Schedule**	**Cycle Length**
Arm A	Dexamethasone in Mucolox™	None	5mL x 0.1mg/mL = 0.5 mg/rinse, 3 times/day =1.5 mg	Oral Rinse, 5 mins. each time (do not swallow)	7 days/week	28 days (4 weeks) One Cycle Only*
Arm B (standard of care)	Dexamethasone solution	None	5mL x 0.1mg/mL = 0.5 mg/rinse, 3 times/day =1.5 mg	Oral Rinse, 5 mins. each time (do not swallow)	7 days/week	28 days (4 weeks) One Cycle Only*

*All subjects will be treated with fluconazole 200 mg once-a-week dosing for prophylaxis (see section 5.5)

9.3 Study Agents Administration

The Investigator or co-investigators will prescribe the study drug in the clinic and instruct the patient on study drug use. Both dexamethasone compounded 0.5mg/5ml solution in Mucolox™ and commercial dexamethasone solution will be dosed topically at a concentration of 0.5 mg/5mL.

A four week supply will be dispensed. The treatment instructions will be to rinse and spit (NOT swallow) with one teaspoon (5 mL) of the solution, three times a day for 5 minutes at a time, and not to eat or drink for 15 minutes afterwards. Subjects will maintain a diary (Appendix 2) and record each dose, the length of time rinsing, and any adverse effects.

9.3.1 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF). The PI or covering clinician will determine whether an adverse event was expected and/or related to study procedures. Study subjects will be asked to report any adverse events or concerns to study staff as they arise.

9.3.2 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

10 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

10.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

1. death
2. a life-threatening adverse experience
3. inpatient hospitalization or prolongation of existing hospitalization
4. a persistent or significant disability/incapacity
5. a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

10.3 Medical Monitoring

Dr. Alessandro Villa should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: 415-476-2431 (office); 415-476-2045 (clinic)

11 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

11.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents (see below for early termination procedures).

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 2) should have an early discontinuation visit. Subjects who withdraw after Visit 1 but prior to Visit 2 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

12 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Non-compliance with study drug regimen

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

Compliance will be monitored closely. Non-compliant patients who use the treatment fewer than 2 times a day for more than 2 weeks (as determined by review of the treatment diary at the week 4 visit) will be considered unevaluable for the primary endpoint and replaced with new patients. These patients, however, will be included in the toxicity report. During the four-week period when patients are receiving study treatment, additions of new immunomodulatory medications (systemic or topical in the mouth) are allowed, but these patients will be regarded as unevaluable for the primary endpoint and will be replaced.

13 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

13.1 Study design/Endpoints

The primary objective of this open label randomized phase II study is to evaluate the efficacy and tolerability of topical compounded dexamethasone solution in a Mucolox™ for the treatment of Oral Inflammatory Ulcerative Diseases. The primary endpoint will be a change from pre to post treatment in each subject's subjective sensitivity score (0-10) evaluated at baseline and 4 weeks post treatment for each arm. We will also compare changes of the daily subject's subjective sensitivity score (0-10) over time for each arm.

The secondary objectives include the evaluation of objective data using the REU scoring system and the oral health related quality of life using the OHIP-14.

13.1.1 Analysis of Primary Endpoints

VAS scores will be summarized descriptively for each arm at pre-treatment, post-treatment, and pre-to-post treatment change. The pre-to-post treatment change will be compared between the arms using either Student's t-test or Mann–Whitney test, depending on the distribution of the data.

13.1.2 Analysis of Secondary Endpoints

Oral health related quality of life will be assessed before and after topical therapy using the 14-item Oral Health Impacts Profile (OHIP-14; see Appendix 5) instrument that measures subject's perceptions of the impact of oral conditions on their well-being. The OHIP-14 scores will be summarized descriptively for each arm at pre-treatment, post-treatment, and pre-to-post treatment change. The pre-to-post treatment change for each item and for all items combined will be assessed within each arm using either paired t test or Wilcoxon-signed-rank test depending on its distribution. In addition, each question will be dichotomized and classified as 'response' if the answer is 'not at all', or 'slightly' to a question such as "how isolated do you feel as a result of this oral condition", and pre-to-post treatment improvement will be assessed using McNemar's test within each arm.

In order to evaluate the clinical improvement in clinician-reported outcome measures for Oral Inflammatory Ulcerative Diseases, REU scores within the compound dexamethasone solution in Mucolox™ group (Arm A) will be compared to that in the dexamethasone solution only group (Arm B). The REU scores will be summarized descriptively for each arm at pre-treatment, post-treatment, and pre-to-post treatment change. The pre-to-post treatment change will be compared between the arms using either student's t-test or Mann–Whitney test, depending on the distribution of the data.

13.2 Sample Size, Accrual Rate and Study Duration

The sample size was calculated based on the data by Rhodus et al., as to ensure at least 80% power and two-sided alpha of 0.05 in detecting a t difference of 2.0 points oral pain on an 11 point scale (VAS 0-10) between Arm A and B[27]. The mean expected change for Arm A will be 6.5 points reduction with a standard deviation of 1.4 points. The mean expected change for Arm B will be 4.5 points reduction with a standard deviation of 1.4 points.

A total of 15 patients per arm will be enrolled (total of 30 subjects). The proposed sample size includes a loss of follow up of 5%. Approximately 60 patients per year are diagnosed with Oral Inflammatory Ulcerative Diseases at the Sol Silverman Oral Medicine Clinic at UCSF. We anticipate the accrual rate will be approximately 2 patients per month, thus the accrual goal will be achieved in approximately 15 months.

13.3 Interim Analysis

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by or the Overall Principal Investigator. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

14 DATA COLLECTION, RETENTION AND MONITORING

14.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at the study site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

14.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

14.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

14.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

14.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

14.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

14.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

15 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked

file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

15.1 Protocol Amendments

Any amendment to the protocol will be written by the PI. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

15.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

15.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of

informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

15.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

15.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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16 APPENDICES

Appendix 1: Patient instructions
Appendix 2: Treatment diary
Appendix 3: Visit #1 CRF
Appendix 4: Visit #2 CRF
Appendix 5: OHIP-14

Appendix 1

INSTRUCTIONS FOR PREPARING & USING YOUR TOPICAL SOLUTION

WHAT YOU WILL RECEIVE

- One 480 mL bottle of concentrated solution (5 mg/5 mL)
- 4 tablets of fluconazole 200 mg

USING YOUR SOLUTION

You will be rinsing with your solution **3 times per day**.

1. Gently shake the bottle of solution.
2. Pour 5 mL of solution into the dosing cups provided.
3. Swish the solution in your mouth for 5 minutes, then spit – DO NOT SWALLOW!
4. Do not eat or drink for 15 minutes after rinsing.

Please take one table of fluconazole once a week

Appendix 2. Treatment Diary

Week	Day/Date	Rinse #1 (check/fill)		Rinse #2 (check/fill)		Rinse #3 (check/fill)		From a scale 0-10, how would you rate your mouth sensitivity today?	Comments
		5 min	Other*	5 min	Other*	5 min	Other*		
1	1								
	2								
	3								
	4								
	5								
	6								
	7								
2	8								
	9								
	10								

	11								
	12								
	13								
	14								

3	15								
	16								
	17								
	18								
	19								
	20								
	21								
4	22								

	23								
	24								
	25								
	26								
	27								
	28								

Appendix 3

DEXAMETHASONE RINSE IN MUCOLOX™ FOR THE TREATMENT OF ORAL INFLAMMATORY ULCERATIVE DISEASES

VISIT #1

Subject Name _____

Medical Record Number _____

Date of Visit _____

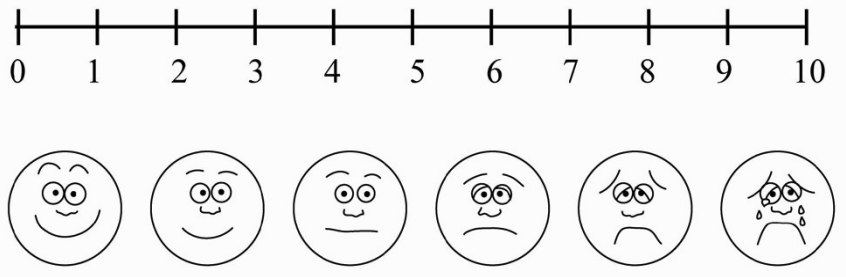
SUBJECTIVE DATA (Over last <u>two weeks</u> unless specified)

MUCOSAL PATHOLOGY

1. Does your mouth hurt now? Y/N

2. Does it hurt to swallow food or drink? Y/N

3. How would you rate your worst mouth sensitivity over the last week**?**



No sensitivity Worst sensitivity

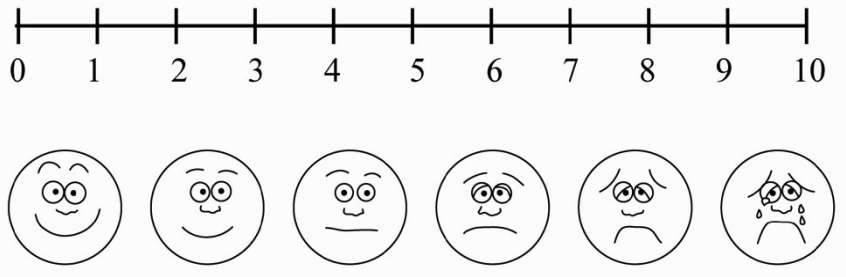
4. Do you avoid any foods because they make your mouth hurt?

   0 = Not at all
   1 = Slightly
   2 = Moderately
   3 = Quite a bit
   4 = Extremely

   If "yes", what types of foods?

   a. Spicy foods
   b. Acidic foods
   c. Salty foods
   d. Hard/crunchy/crusty foods
   e. Other:

5. Do you feel that your oral intake (what you eat) is limited by your oral condition? Y/N



Not limited at all Severely limited

   Score: _____

   If "Yes", how limited do you feel it is?

   a. Partial limitation
   b. Severe limitation

6. Have you been bothered by ulcers in the mouth?

   0 = Not at all
   1 = Slightly
   2 = Moderately
   3 = Quite a bit
   4 = Extremely

OBJECTIVE DATA (REU score)

Site	*Reticular area*		*Erythematous area*			*Ulcerative area*			
Upper/lower labial mucosa	0	1	0	1	2	3	0	1	2	3
Right buccal mucosa	0	1	0	1	2	3	0	1	2	3
Left buccal mucosa	0	1	0	1	2	3	0	1	2	3
Dorsal tongue	0	1	0	1	2	3	0	1	2	3
Ventral tongue	0	1	0	1	2	3	0	1	2	3
Floor of mouth	0	1	0	1	2	3	0	1	2	3
Hard palate mucosa	0	1	0	1	2	3	0	1	2	3
Soft palate/tonsillar pillars	0	1	0	1	2	3	0	1	2	3
Maxillary gingiva	0	1	0	1	2	3	0	1	2	3
Mandibular gingiva	0	1	0	1	2	3	0	1	2	3
Total										

(R: 0 = not present, 1 = present; E & U: 0 = not present, 1 = <1cm^2, 2 = 1 - 3cm^2, 3 = >3cm^2)

Total Score:

Total Weighted Score:

PHOTOGRAPHS TAKEN (circle): YES NO

Appendix 4

DEXAMETHASONE RINSE AND MUCOLOX™ FOR THE TREATMENT OF ORAL INFLAMMATORY ULCERATIVE DISEASES

VISIT #2

Subject Name _____

Medical Record Number _____

Date of Visit _____

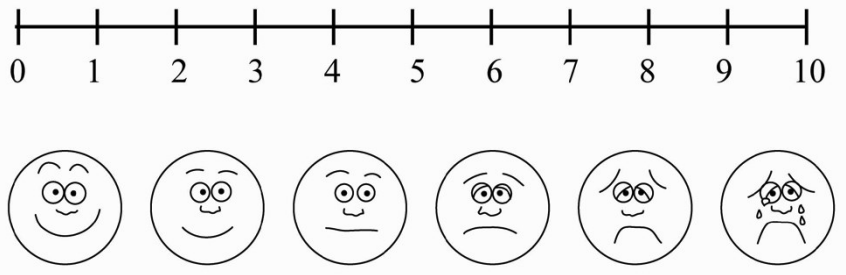
SUBJECTIVE DATA (Over last <u>one week</u> unless specified)

MUCOSAL PATHOLOGY

1. Does your mouth hurt now? Y/N

2. Does it hurt to swallow food or drink? Y/N

3. How would you rate your worst mouth sensitivity over the last week**?**



No sensitivity Worst sensitivity

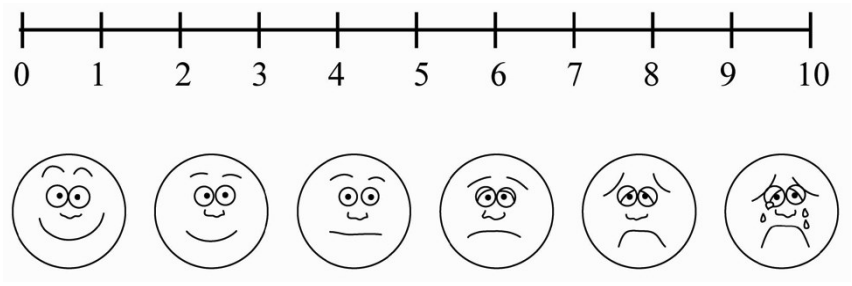
4. Do you avoid any foods because they make your mouth hurt?

0 = Not at all
1 = Slightly
2 = Moderately
3 = Quite a bit
4 = Extremely

If "yes", what types of foods?

a. Spicy foods
b. Acidic foods
c. Salty foods
d. Hard/crunchy/crusty foods
e. Other:

5. Do you feel that your oral intake (what you eat) is limited by your oral condition? Y/N



Not limited at all Severely limited

Score: _____

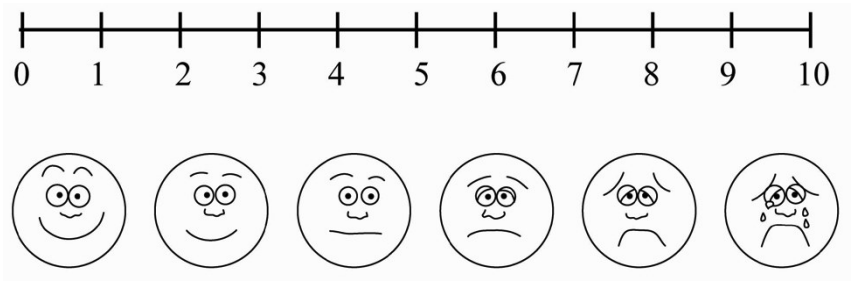
If "Yes", how limited do you feel it is?

a. Partial limitation ☐
b. Severe limitation ☐

6. Have you been bothered by ulcers in the mouth?

0 = Not at all
1 = Slightly
2 = Moderately
3 = Quite a bit
4 = Extremely

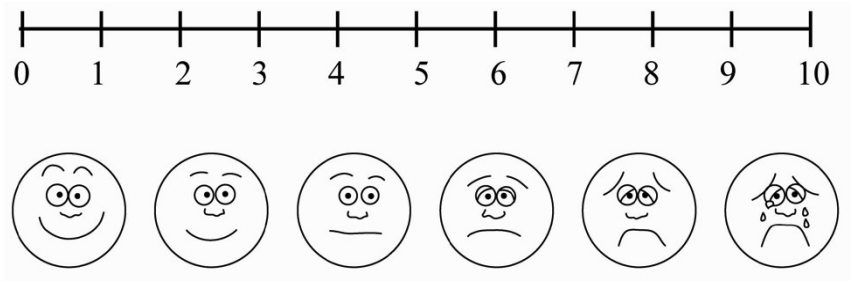
7. Rate your level of comfort while rinsing with the topical therapy:



Not uncomfortable at all Very uncomfortable

Score: _____

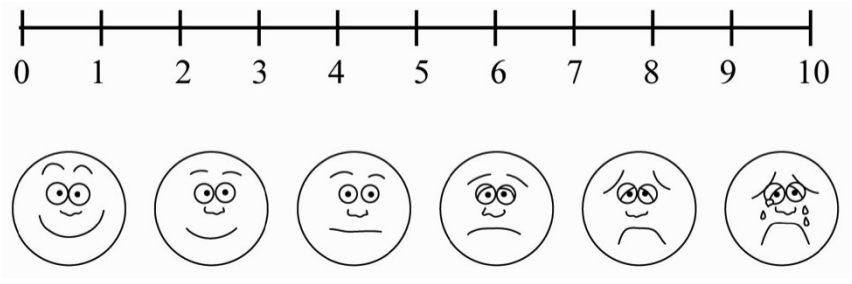
8. Rate the taste of the topical treatment:



Very good taste Very bad taste

Score: _____

9. Rate how your mouth feels since starting topical therapy:



Mouth feels much better Mouth feels much worse

Score: _____

10. Overall, since beginning topical therapy, my mouth is: (Check one)

- ☐ Very much better
- ☐ Moderately better

- A little better
- About the same
- A little worse
- Moderately worse
- Very much worse

OBJECTIVE DATA

Site	*Reticular area*		*Erythematous area*			*Ulcerative area*			
Upper/lower labial mucosa	0	1	0	1	2	3	0	1	2	3
Right buccal mucosa	0	1	0	1	2	3	0	1	2	3
Left buccal mucosa	0	1	0	1	2	3	0	1	2	3
Dorsal tongue	0	1	0	1	2	3	0	1	2	3
Ventral tongue	0	1	0	1	2	3	0	1	2	3
Floor of mouth	0	1	0	1	2	3	0	1	2	3
Hard palate mucosa	0	1	0	1	2	3	0	1	2	3
Soft palate/tonsillar pillars	0	1	0	1	2	3	0	1	2	3
Maxillary gingiva	0	1	0	1	2	3	0	1	2	3
Mandibular gingiva	0	1	0	1	2	3	0	1	2	3
Total										

(R: 0 = not present, 1 = present; E & U: 0 = not present, 1 = <1cm^2, 2 = 1 - 3cm^2, 3 = >3cm^2)

Total Score:

Total Weighted Score:

PHOTOGRAPHS TAKEN (circle): YES NO

Appendix 5. OHIP-14

	Never (0)	Hardly Ever (1)	Occasionally (2)	Fairly Often (3)	Very Often (4)
FUNCTIONAL					
Have you had trouble *pronouncing any words* because of problems with your teeth, mouth, or dentures?					
Have you felt that your *sense of taste* has worsened because of problems with your teeth, mouth, or dentures?					
PHYSICAL PAIN					
Have you had *painful aching* in your mouth?					
Have you found it *uncomfortable to eat any foods* because of problems with your teeth, mouth, or dentures?					
Psychological Discomfort					
Have you been *self-conscious* because of problems with your teeth, mouth, or dentures?					
Have you *felt tense* because of problems with your teeth, mouth, or dentures?					
PHYSICAL DISABILITY					
Has your *diet been unsatisfactory* because of problems with your teeth, mouth, or dentures?					

Have you had to *interrupt meals* because of problems with your teeth, mouth, or dentures?					
PSYCHOLOGICAL DISABILITY					
Have you found it *difficult to relax* because of problems with your teeth, mouth, or dentures?					
Have you been a bit *embarrassed* because of problems with your teeth, mouth, or dentures?					
SOCIAL DISABILITY					
Have you been a bit *irritable with others* because of problems with your teeth, mouth, or dentures?					
Have you had *difficulty doing your usual jobs* because of problems with your teeth, mouth, or dentures?					
HANDICAP					
Have you felt that life in general was *less satisfying* because of problems with your teeth, mouth, or dentures?					
Have you been totally *unable to function* because of problems with your teeth, mouth, or dentures?					