NCT02850601 Dexamethasone Solution for the Treatment of Oral Lichen Planus

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TITLE: Dexamethasone solution and Dexamethasone in Mucolox™ for the Treatment of Oral Lichen Planus

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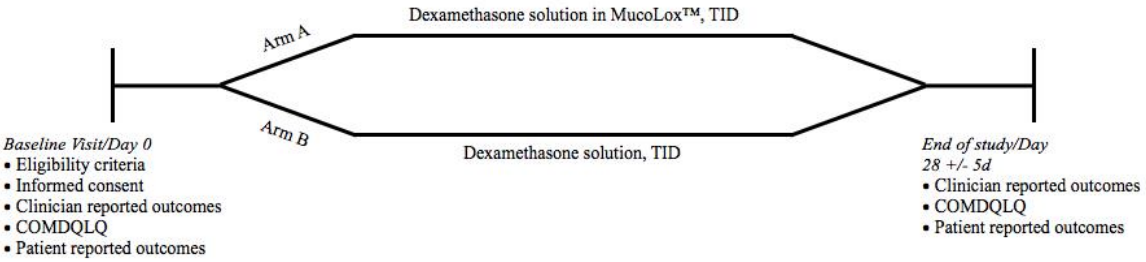
Agent(s): Mucolox™ (PCCA, Houston, TX 77099); dexamethasone 0.5mg/5mL solution (NDC 00054-3177-57; West-Ward pharmaceuticals Corp., Eatontown, NJ 07724); dexamethasone sodium phosphate USP powder (PCCA, Houston, TX, 77099, part# 55-1430, CAS# 2392-39-4)

TABLE OF CONTENTS

SCHEMA


Dexamethasone solution in MucoLox™, TID
Arm A
Arm B
Dexamethasone solution, TID
Baseline Visit/Day 0
• Eligibility criteria
• Informed consent
• Clinician reported outcomes
• COMDQLQ
• Patient reported outcomes
End of study/Day
28 +/- 5d
• Clinician reported outcomes
• COMDQLQ
• Patient reported outcomes

1. BACKGROUND AND SIGNIFICANCE

1.1 Oral lichen planus

Oral lichen planus (OLP) is a common benign, chronic immune-mediated inflammatory 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.

1.1.1 Management of oral lichen planus

Available therapies for OLP are not curative, but 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[1,5,6]. 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[7-12].
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 OLP, 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[13]. 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 lichen planus may lead to the development of secondary candidiasis in 11-47% of patients, which requires antifungal therapy[10,14,15]. Antifungal drug therapy, such as fluconazole has been showed to be an effective prophylaxis measure to prevent oral candidiasis

infection[16-18]. 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[19-21]. 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[22]. 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[22,23].

1.2 Dexamethasone solution for oral lichen planus

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[24]. 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[25]. 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 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.

1.3 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[26,27]. 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.

1.4 Significance

There is a significant unmet need for optimized topical therapies for oral lichen planus. Topical steroid therapy is considered the first line of treatment for oral lichen planus with current treatment regimens requiring multiple application or rinses daily[24,28,29]. 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.

2. SPECIFIC AIMS

The objective of this single center, 4-week, open label randomized, phase II study is to evaluate and characterize the tolerability and clinical effectiveness of dexamethasone 0.5mg/5ml solution in a mucoadhesive vehicle (Mucolox™) for the treatment of oral lichen planus. 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™. If significant benefits are noted, this approach could be applied to the management of other oral mucosal immune-mediated conditions, such as graft-versus-host disease and mucous membrane pemphigoid.

2.1 Study Design

This is a single center, 4-week, open label randomized, phase II study. Randomization will be conducted by the BWH Investigational 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 compound dexamethasone in Mucolox™ or dexamethasone only. Subjects will return for evaluation after four weeks at which time the primary end-points will be assessed.

2.2 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 lichen planus as measured by a reduction in oral symptoms between patients treated with commercial dexamethasone 0.5mg/5ml solution in Mucolox™ (group A) and patients treated with topical dexamethasone 0.5mg/5ml solution only (group B).

2.3 Secondary Objective

The secondary objectives are:

- To determine the clinical improvement in clinician-reported outcome measures achieved by treatment with topical compound dexamethasone at 0.5 mg/5 mL in Mucolox™ compared to dexamethasone 0.5mg/5ml solution alone.
- To assess the tolerability of oral lichen planus as measured with the chronic oral mucosal diseases quality of life questionnaire (COMDQLQ).

2.4 Hypothesis

Dexamethasone solution (0.5mg/5ml) in Mucolox™ when swished for 5 minutes and expectorated three times daily, is *well-tolerated* and *more effective* than dexamethasone solution (0.5 mg/5 mL) alone in the management of oral lichen planus.

2.5 Specific Aim

In order to evaluate the hypothesis, the specific aim for this study is:

2.5.1 To compare the clinical outcome with a primary endpoint of reduction in oral symptoms between patients treated with dexamethasone 0.5mg/5ml solution in Mucolox™ (group A) and patients treated with topical dexamethasone 0.5mg/5ml solution only (group B).

3. SUBJECT SELECTION

3.1 Eligibility Criteria

3.1.1 Age 18 years and older.

3.1.2 Patients with symptomatic oral lichen planus (worst VAS sensitivity score ≥ 7 over the last week).

3.1.3 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients already on topical or systemic steroids.

3.2.2 Inability to comply with study instructions.

3.2.3 Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.4 VAS sensitivity score < 7.

3.2.5 Pregnant women. A urine pregnancy test will be performed for women of child bearing potential.

3.2.6 Allergy to fluconazole, clotrimazole or nystatin.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. SUBJECT ENROLLMENT

The Division of Oral Medicine and Dentistry at Brigham and Women's Hospital is a major referral center for oral medicine patients including patients with oral lichen planus. Clinical diagnosis of oral lichen planus will be made by the patient's oral medicine specialist. Patients with a confirmed clinical diagnosis of oral lichen planus and with oral symptoms (defined as the worst VAS sensitivity score ≥7 over the last week) will be eligible to participate 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 (see Appendix). Those answering with at least a score of "7" (1/10) and that meet all other eligibility requirements (see section 3.0) 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.

4.1 Procedures for obtaining informed consent

All patients will sign an informed consent. Patients will be informed that they have equal chances of being assigned to one of two groups. Patients will be told what personal identifying information will need to be collected, and the privacy rights of study participants will be explained. The consenting physician will ensure that the patient is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study, with the clear understanding that participation is optional. Patients will be encouraged to ask questions and will have the opportunity to take the consent form with them and review before making a decision whether or not to participate. Patients will also be notified that they are free to discontinue participation in the study at any time. By signing the consent form, potential subjects agree to participate in the study. If consent is withdrawn during the study, no further measurements will be conducted.

4.2 Treatment assignment and randomization

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

5. 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 (see Appendix). Those answering with at

least a score of "7" (1/10) and that meet all other eligibility requirements (see Section 3) 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 BWH 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 lichen planus.

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 compound dexamethasone 0.5mg/5ml solution in Mucolox™ (ARM A) or 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 end-points will be assessed.

Clotrimazole or Nystatin will be prescribed as an alternative antifungal drug in the event of fluconazole allergy.

If there is worsening of oral lichen planus 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 $\pm$ 5 days (end of study)
Clinical examination	x	x
COMDQLQ	x	x
Patient Reported Outcomes	x	x

5.1.1 Clinician Reported Outcomes

Mucosal disease will be measured using the REU scoring system for monitoring oral lichen planus[30]. 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 site are then totaled.

Intraoral photographs will be obtained at each visit.

5.1.2 Chronic Oral Mucosal Diseases Quality of Life Questionnaire

Patients will complete the 24-item Chronic Oral Mucosal Diseases Quality of Life Questionnaire (COMDQLQ) instrument at baseline and at the end of treatment[31]. 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 lichen planus.

5.1.3 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 oral lichen planus (see Appendix 2&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 Treatment diary). Tolerability and compliance will also be evaluated, and a patient reported global assessment of overall improvement will be evaluated at the four-week visit.

5.2 Treatment Regimen

A four week supply of compound 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 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 antifungal dosing for prophylaxis (see section 5.5)

5.3 Study Agents Administration

The Investigator or co-investigators will prescribe the study drug in the clinic via Epic and instruct the patient on study drug use. Both dexamethasone compound 0.5mg/5ml solution in Mucolox™ and 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 and record each dose, the length of time rinsing, and any adverse effects.

5.4 Drug Accountability

Patients will be instructed to bring empty bottles of study drug at the final visit. Adherence with the prescribed study treatment regimen will be determined by reviewing the study diary and returned bottles.

5.5 General Concomitant Medication and Supportive Care Guidelines

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.

Clotrimazole or nystatin will be prescribed as an alternative antifungal drug in the event of fluconazole

allergy. Clotrimazole 10 mg troche (lozenge) to be dissolved in the mouth four times a day for four weeks; or nystatin 100,000 unit/mL oral suspension to rinse for one minute, swish and spit, four times a day for four weeks.

Possible side effects of fluconazole include nausea, vomiting and headache. Possible side effects of nystatin oral suspension include rash, diarrhea, nausea, oral irritation, vomiting. Possible side effects of clotrimazole troche (lozenge) include abnormal sensation in the mouth, loss of appetite, diarrhea, nausea, vomiting, abnormal liver function tests.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Subjects will be taken off protocol therapy for any of the following reasons:

- If the principal investigator feels it is in their best interest
- If the subject cannot tolerate the study rinses
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

Subjects may be removed from the study in favor of clinical care should their symptoms worsen or should they have an adverse reaction to the study drug.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI Alessandro Villa, DDS, PhD, MPH at 617-732-5517 (p36572).

5.7 Duration of Follow Up

There is no follow-up period after completing the four-week treatment period.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, will be documented in the case report form (CRF).

6. BIOSTATISTICAL ANALYSIS

6.1 Study design/Endpoints

The primary objective of this open label randomized phase II study is to evaluate the efficacy and tolerability of topical compound dexamethasone solution in a Mucolox™ for the treatment of oral lichen planus. 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 24-item Chronic Oral Mucosal Diseases Quality of Life Questionnaire. For the analysis of secondary endpoints see section 6.5.

6.2 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[24]. 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 12 patients per arm will be enrolled (total of 24 subjects). The proposed sample size includes a loss of follow up of 5%. Approximately 75 patients per year are diagnosed with oral lichen planus at the Division of Oral Medicine and Dentistry (BWH)[32]. We anticipate the accrual rate will be approximately 5 patients per month, thus the accrual goal will be achieved in approximately five months.

6.3 Interim Monitoring Plan

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by BWH or the BWH

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.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion

6.3.1 Monitoring of Adverse Events

All adverse events will be reviewed by the principal investigator or covering clinician. In accordance with PHRC guidelines, 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.

6.3.2 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents will be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol will be submitted as amendments and will be approved by the IRB prior to implementation. Any changes in study conduct will be reported to the IRB. The BWH Overall Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study will be made in writing.

6.4 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.

6.5 Analysis of Secondary Endpoints

Oral health related quality of life will be assessed before and after topical therapy using the 24-item Chronic Oral Mucosal Diseases Quality of Life Questionnaire (COMDQLQ; see Appendix) instrument that measures subject's perceptions of the impact of oral conditions on their well-being. The COMDQLQ 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 lichen planus, 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.

6.6 Reporting and Exclusions

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.

6.6.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment. All toxicities will be monitored closely.

Development of grade III-IV treatment related toxicity will be monitored closely. If we observe 3 or more patients with grade III-IV treatment related toxicity, the study will be terminated.

7. DOSING DELAYS/DOSE MODIFICATIONS

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the final study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

There will be no dosing delays/modifications.

8. RISKS AND DISCOMFORTS

8.1 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 either fluoconazole, clotrimazole or nystatin (see

section 5.5). 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 (see section 11.1.1).

9. POTENTIAL BENEFITS

9.1 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.

9.2 Potential benefits to society

The results of this study have the potential to impact clinical guidelines for the management of oral lichen planus.

10. MONITORING AND QUALITY ASSURANCE

10.1 Safety monitoring

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 or patient Gateway 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 (see below).

10.2 Adverse events

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. This study follows Partners Health Care guidelines regarding the definitions and reporting policies of adverse events. The following list of reported and/or potential AEs (Section 10.3) and the characteristics of an Expected Toxicity (Section 10.4) will determine whether the event requires expedited reporting **in addition** to routine reporting.

10.3 Reported and/or potential AE

AE include development of secondary oral candidiasis and short-term hypothalamic-pituitary-adrenal axis alteration (e.g., Cushingoid symptoms), although rare.

10.4 Expected Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear above and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

Some expected toxicities include: transient burning, and the development of secondary oral candidiasis (which will be minimized with prophylactic antifungal drug therapy).

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[33]. 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 Mucolox™ and/or dexamethasone solution when used as a swish and spit.

10.5 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** 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.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.6 Expedited Adverse Event Reporting

10.6.1 Investigators will report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

10.7 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

10.8 Routine Adverse Event Reporting

All Adverse Events **will** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) will <u>also</u> be reported in routine study data submissions.**

11. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 10.

11.1 Mucolox™

11.1.1 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		
Sodium Hyaluronate	Sodium Hyaluronate		
Poloxamer 407	Poloxamer 407		
Zea Mays (Corn) Starch	Zea Mays (Corn) Starch		
Carbomer	Carbomer		
Water			

11.1.2 Compatibility

N/A

11.1.3 Handling

There are no special handling requirements.

11.1.4 Availability

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

11.1.5 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 compound 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

11.1.6 Administration

Subjects will be instructed to rinse with 5 ml of compound 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.

11.1.7 Ordering

Study rinses will be ordered through the BWH Investigational Pharmacy via EPIC.

11.1.8 Accountability

A study diary will be given to the subject where they will be asked to check off each rinse completed, with three check boxes per day on study (Appendix 2).

11.1.9 Destruction and Return

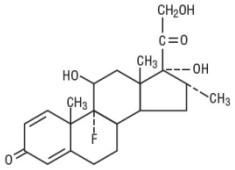
Patients should not continue to use any unused study supply once they have completed the study. It should be returned to the investigator and will be sent to pharmacy for destruction.

11.2 Dexamethasone solution

11.2.1 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.

11.2.2 Storage and Stability

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

11.2.3 Compatibility

N/A

11.2.4 Handling

There are no special handling requirements.

11.2.5 Availability

Dexamethasone 0.5mg/5mL solution will be dispensed through the BWH Investigational Pharmacy.

11.2.6 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

11.2.7 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.

11.2.8 Ordering

Dexamethasone solution will be ordered through the BWH Investigational Pharmacy via EPIC.

11.2.9 Accountability

A study diary will be given to the subject where they will be asked to check off each rinse completed, with three check boxes per day on study (Appendix 2).

11.2.10 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.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0

12.1 Monitoring and quality assurance

Safety monitoring

The safety of participants and the overall study will be monitored continuously throughout the study period. Evaluating physicians will query participants for any adverse events and review 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 (see above).

13. PUBLICATION PLAN

The principal investigator holds the primary responsibility for publication of the study results. The results will be presented in abstract form at a national/international and/or oral medicine conference and will be published in a peer reviewed journal.

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251.

APPENDICES

Appendix 1: Patient instructions

Appendix 2: Treatment diary

Appendix 3: Visit #1 CRF

Appendix 4: Visit #2 CRF

Appendix 5: COMDQLQ

INSTRUCTIONS FOR PREPARING & USING YOUR TOPICAL SOLUTION

WHAT YOU WILL RECEIVE

- One 480 mL bottle of concentrated solution (5 mg/5 mL)

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.

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								

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*		
3	15								
	16								
	17								
	18								
	19								
	20								
	21								
4	22								
	23								
	24								

	25								
	26								
	27								
	28								

DEXAMETHASONE RINSE AND MUCOLOX™ FOR THE TREATMENT OF ORAL LICHEN PLANUS

VISIT #1

Subject Name _____

Medical Record Number _____

Date of Visit _____

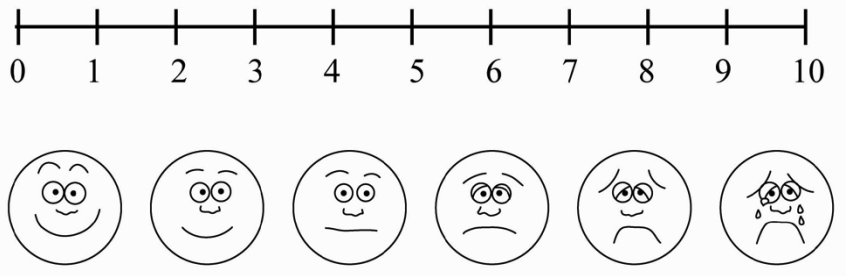
SUBJECTIVE DATA (Over last <u>two weeks</u> unless specified)

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

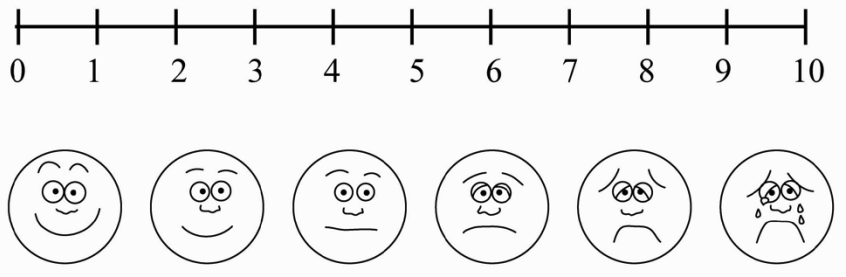
4. Do you avoid any foods because they make your mouth hurt?

   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

DEXAMETHASONE RINSE AND MUCOLOX™ FOR THE TREATMENT OF ORAL LICHEN PLANUS

VISIT #2

Subject Name _____

Medical Record Number _____

Date of Visit _____

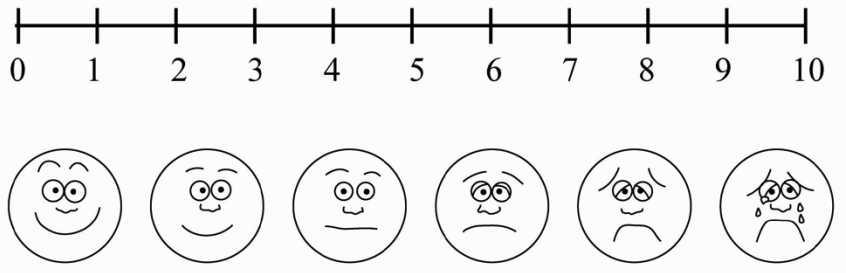
SUBJECTIVE DATA (Over last <u>one week</u> unless specified)

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?

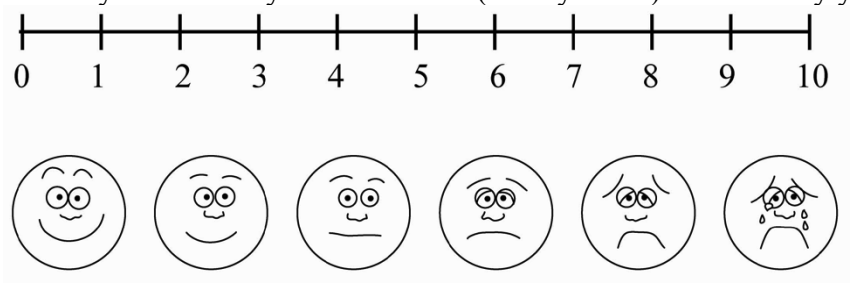
   0 = Not at all
   1 = Slightly
   2 = Moderately
   3 = Quite a bit
   4 = Extremely

   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: _____

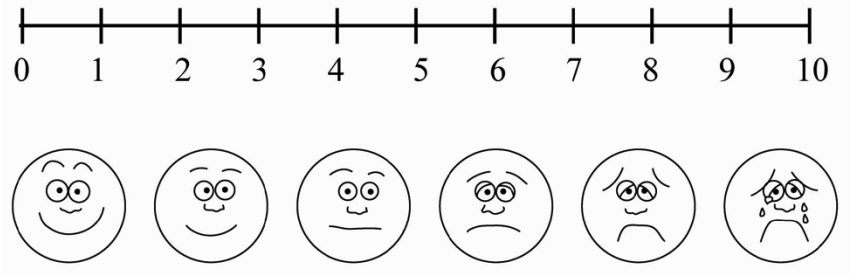
If "Yes", how limited do you feel it is?

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

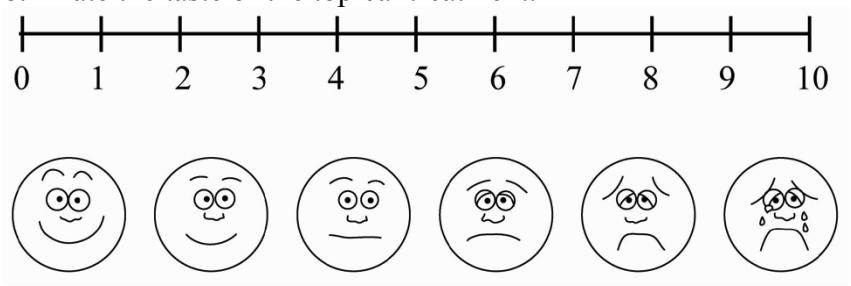
7. Rate your level of comfort while rinsing with the topical therapy:



Not uncomfortable at all Very uncomfortable

Score: _____

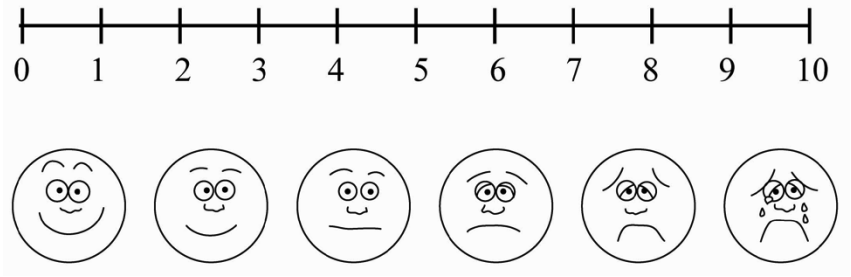
8. Rate the taste of the topical treatment:



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

COMDQLQ

	Not at all (0)	Slightly (1)	Moderately (2)	Considerably (3)	Extremely (4)
Pain and functional limitation					
How much do certain types of food/drink cause you discomfort (spicy food, acidic food)?					
How much does your oral condition cause you to limit the types of food/ drinks you consume?					
How much do certain food textures cause you discomfort (rough food, crusty food)?					
How much does your oral condition cause you to limit the textures of the food you consume?					
How much does the temperature of certain foods/drinks cause you discomfort?					
How much does you oral condition cause you to limit the temperature of the foods/ drinks you consume?					
How much does your oral condition lead to discomfort when carrying out your daily oral hygiene routine (brushing, flossing, mouthwash usage)?					
How much does your oral condition cause you to limit your daily oral hygiene routine (brushing, flossing, mouthwash usage)?					
How much does your oral condition lead to discomfort when wearing a denture (false teeth)?					
Medication and treatment					
How much do you feel you need medication to help you with activities of daily life (talking, eating, etc.)?					
How satisfied are you with the medication being used to treat your oral condition?					
How concerned are you about the possible side effects of the medications used to treat your oral condition?					
How much does it frustrate you					

that there is no single standard medication to be used in your oral condition?					
How much does the use of the medication limit you in your everyday life (routine/the way you apply or take your medications)?					
How much does it bother you that there is no cure for your oral condition?					
Social and emotional					
How much does your oral condition you down?					
How much does your oral condition cause you anxiety?					
How much does your oral condition cause you stress?					
How much does the unpredictability your oral condition bother you?					
How much does your oral condition cause you to worry about the future (spread of the condition, possible cancer risk)?					
How much does your oral condition make you pessimistic about the future?					
How much does your oral condition disrupt social activities in your life (social gatherings, eating out parties)?					
Patient support					
How satisfactory do you consider the information available to you regarding your oral condition?					
How satisfied are you with the level of support and understanding shown to you by family regarding this oral condition?					
How satisfied are you with the level of support and understanding shown to you by friends/work colleagues regarding your oral condition?					
How isolated do you feel as a result of this oral condition?					