Neoadjuvant Imiquimod for Oral Cancer

Protocol Number: 103625

National Clinical Trial (NCT) Identified Number: 04883645

Principal Investigator: Angela Yoon, DDS

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
All	Organization change	Dr. Yoon relocated from Columbia University to MUSC.
3, 9	Addition of tumor cell quantification using immunofluorescence in the primary endpoint assessment Additional statistical analyses as required	Expansion of laboratory techniques to evaluate primary endpoint

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STATEMENT OF COMPLIANCE

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

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

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

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

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Exploratory clinical trial of topical Imiquimod 5% cream as window-of-opportunity monotherapy for early-stage oral cancer
Study Description:	Our aim is to conduct an exploratory clinical trial to assess the efficacy of neoadjuvant imiquimod immunomodulatory topical therapy in reducing the size of primary oral cancer and evaluate its safety and toxicity in early-stage oral cancer patients.
Objectives:	**Primary Objective:** To assess the preliminary efficacy of topical imiquimod in neoadjuvant setting in patients with early-stage oral squamous cell carcinoma as determined by a minimum of 50% reduction in tumor assessed first by pathologic review and then confirmed with tumor cell count using quantitative immunofluorescence. **Secondary Objective:** To assess local and systemic safety and tolerability by CTCAE v5 criteria. **Exploratory Objective:** To explore the effect of imiquimod on the tumor immune microenvironment (immune profile) by performing quantitative multiplex immunofluorescence.
Endpoints:	**Primary Endpoint**: The primary endpoint is the overall ***clinical and histological*** response rate as defined as the precent reduction in tumor size obtained by measuring the longest perpendicular bidirectional size of the clinically visible lesion, and the percent change in tumor cell count assessed first by pathologic review and then confirmed with tumor cell count using quantitative immunofluorescence , confirmed at 4 weeks of the start of study therapy. **Secondary Endpoints**: The secondary endpoint is defined as safety and toxicity assessed using CTCAE v5.0 criteria.
Study Population:	A total of 15 subjects will be accrued. We will accrue oral squamous cell carcinoma (OSCC) patient ≥18 years old, with biopsy confirmed OSCC, assigned to clinical stage I or II, awaiting surgical excision and who have an ECOG performance status of ≤2 at MUSC, South Carolina.
Phase:	0 (Exploratory)
Description of Sites/Facilities Enrolling Participants:	This is an open-label, single-center clinical trial that will be conducted in Hollings Cancer Center at MUSC.

Description of Study Intervention:	Off-label use of imiquimod 5% topical cream: The patient will be instructed to apply imiquimod cream, 7 nights a week for 28 days to the oral tumor at bedtime. Instructions will also include application of cream in the surrounding area extending at least 2 cm beyond the outlined tumor margins to cover potentially cancerized field.
Study Duration:	2-years
Participant Duration:	1 month

1.2 SCHEMA

Days -14 to -1 Screening Visit

- Phone call (PI): Reach out to patients with histologic confirmation of OSCC, ensure patient is not immunocompromised or on immunosuppressive medication, otherwise in good health or have conditions well managed by medication; if eligible, ask the patient to come in for a screening visit, email informed consent
- Screening visit: Review and obtain informed consent, complete demographic/medical history form, prior/active medication form; oral examination (no other tumor should be present), take cinical photo, measure tumor size; provide instruction for imiquimod application & daily diary form. *This is to be completed prior to initiation of the study drug on Day 1.
- (SOC) Head & Neck initial consultation: Schedule for the surgery ~4 weeks from Day 1
- Blood draw (CBC): SOC as a part of H&N consult. Obtain and keep record of baseline CBC for comparison with that at the endpoint (immiediately prior to surgery); if the patient is a women of child bearing potential, pregnancy test is to be performed to meet the eligibility criteria (cost covered by the study)
- Request research pharmacy to dispense imiquimod 5% cream (28 packets)

Day 1 Baseline (Day 1) Televisit

- Ask the patient to start medication and contact PI if there are any side effects

Day 14 (+/- 5 days) Midpoint (Day 14) Cinic Visit

- Oral examination, tumor measurements, and take photo
- Check adverse events

Day 29 (+/- 5 days) Endpoint (Day 29) Televisit

- Oral examination, tumor measurements, and take photo
- Adverse events form
- Concomitant medication form
- Collect Daily Diary form
- Compliance form
- Collect remaining medication and send to the research pharmacy

Day 60 (+/- 7 days) One-Month Follow-up phone call

- Check for ongoing adverse events
- Concomitant medication

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Days -14 to -1* Screening Visit	Day 1 (Televisit)	Day 14 (+/-5)*	Day 29 (+/-5)*	Day 30 (+/-14)	Day 60 (+/-7)
Histology confirmation of OSCC in the biopsy specimen (SOC)	x					
Inclusion/Exclusion Criteria	x					
Informed Consent	x					
Demographics/Medical History	x					
Prior/Active Medication Review	x					
Blood draw (CBC); Serum pregnancy test if women of childbearing potential)	X (SOC for CBC)				x (SOC)	
H&N Surgical Consult	x (SOC)					
Baseline Symptoms Form	x					
Physical Symptoms Form	x					
Oral Examination/Tumor measurements/Photography	x		x	x		
Treatment Administration		**Topical Imiquimod 5% cream application (Days 1-28)** (Apply one single-use packet daily before bed)				
Adverse Events Form			x	x		x
Daily Diary Form				x		
Concomitant Medication Form				x		x
Compliance Form				x		
Surgical Resection					x (SOC)	

*Days -14 to -1: Excludes weekends (Saturday, Sunday) and holidays

*+/-5 days for Day 14 and Day 29: Excludes weekends (Saturday, Sunday) and holidays

2 INTRODUCTION

2.1 STUDY RATIONALE

Our overall goal is to discover the most efficacious treatment regimen for patients with early-stage (TNM Stages I/II) oral squamous cell carcinoma (OSCC). Since 80% of oral cancer patients are in early stage at the time of diagnosis[2], there exists a window of opportunity in which accurate prognostication and subsequent decisions for appropriate treatment will dramatically improve the 5-year survival of patients with this deadly disease.

For early-stage oral cancer patients, the five-year survival rate is estimated to be 60%[7]. We are currently developing a microRNA-based prognostic model to distinguish the 40% who will die of the disease from the 60% who will most likely survive[15]. However, treatment modalities for those at a high risk for cancer-specific mortality remains unexplored. It is imperative to discover effective therapy for the early-stage oral cancer patients who have a poor prognosis and are at a high cancer-specific mortality risk following standard surgical treatment.

To address these critical gaps, we propose to assess the efficacy of a topical imiquimod 5% cream in an exploratory clinical trial as a 'window-of-opportunity' monotherapy, administered between the biopsy confirmation of OSCC and the initial tumor surgery. Imiquimod is an FDA-approved Toll-like receptor agonist (TLR)[16-25]. We have previously reported that intra-oral application of topical imiquimod resulted in complete resolution of malignant melanoma with minimal adverse events and the patient had a recurrence-free 5-year survival[22]. Imiquimod can induce tumor cell apoptosis and necrosis, and activate anti-tumoral immune response[16-25].

A topically applicable therapeutic agent has the advantage in that there is minimal systemic absorption, hence, it is well tolerated with negligible systemic adverse events[28]. It can also be applied directly on the oral tumor and adjacent tissue to control the cancerized field, thereby decreasing the rate of local recurrence, the primary culprit of oral cancer-related death following initial surgery. To this end, imiquimod has demonstrated efficacy and safety in cancerized field treatment, showing promise for reducing the incidence of recurrences, thereby increasing overall survival[43].

We propose an exploratory clinical trial to evaluate the efficacy of topical imiquimod, a TLR-7 agonist, in patients with early-stage oral squamous cell carcinoma. The analysis of pre- and post-treatment tumor specimen collected from patients treated on this study will be used for quantitative immunofluorescence analysis to assess the immunomodulatory activity of imiquimod in human tumor samples. We hypothesize that TLR-7 stimulation will reduce the size of the tumor in patients with early-stage oral squamous cell carcinoma. We anticipate that activation of CD4+ T-cell and macrophage will correlate with response to therapy.

2.2 BACKGROUND

Topical imiquimod 5% cream is a FDA-approved TLR (Toll-like receptor) agonist. Imiquimod immune-modulatory therapy has aroused considerable cancer clinical research interest and showed promising results in clinical trials. Imiquimod induces apoptosis and necrosis of tumor cells. Imiquimod-induced necrosis of OSCC cells leads to release of high mobility group box 1 (HMGB1) protein, which in turn acts as a chemokine and induces a pro-inflammatory response[16-24]. Given that a wide variety of genetic and epigenetic defects can suppress apoptosis in most cancers, therapeutic agents with the ability to induce tumor necrosis are advantageous[16]. Imiquimod also initiates tumor cell apoptosis by shifting the pro- and anti-apoptotic Bcl factors toward the pro-apoptotic Bax protein, and by stimulating the release of mitochondrial cytochrome c into the cytosol, activating caspase-9 and caspase-3[21-23]. Indeed, a study showed that imiquimod increased both apoptosis and necrosis of OSCC cells (32.03% and 15.23%, respectively)[24].

Moreover, imiquimod is an immune response modifier, activating macrophages and other cells via TLR7. Imiquimod provokes Th1 cell-mediated immune response by inducing the secretion of proinflammatory cytokines such as interferon-α (IFN-α), tumor necrosis factor-α (TNF-α) and interleukin-12 (IL-12)[23-25]. Currently, imiquimod as a 5% cream is being used to treat several skin cancers, including malignant melanoma, basal cell carcinoma (BCC) and SCC[26-28]. With respect to SCC treatment, it has been demonstrated that imiquimod stimulates tumor destruction by recruiting cutaneous effector T cells from blood and by inhibiting tonic anti-inflammatory signals within the tumor[29]. Other evidence shows that topical imiquimod treatment attenuates the de novo growth of UV-induced SCC through activation of Th17/Th1 cells and cytotoxic T lymphocytes[30]. While surgical excision is the first line treatment, imiquimod has been shown to be an efficacious, non-invasive topical treatment modality, especially when utilized in the neoadjuvant setting prior to initial surgery. Taken together, imiquimod is a promising agent in the treatment of squamous cell carcinoma involving oral mucosa.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Application site reactions:

- Redness, itching, burning, or bleeding of the treated area (33%)
- flaking, scaling, dryness, or thickening of the skin (33%)
- swelling, stinging, or pain in the treated area (33%)
- blisters, scabs, or bumps on the skin (33%)
- inflammation or swelling of the tissue lining the sinuses (7%)
- headache (11%)
- diarrhea (3%)
- red and itchy skin reaction (2%)
- back pain (1%)
- tiredness (1%)
- irregular and rapid heat rate (1%)

- virus infection (1%)
- dizziness (1%)
- vomiting (1%)
- infection of any part of urinary system (1%)
- fever (1%)
- tremor caused by a chill (1%)

Systemic side effects:

- Flu-like symptoms such as nausea, fever, chills, tiredness, and muscle weakness or pain (15%)

Women of child-bearing potential: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Imiquimod cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding: Women using imiquimod should not breast-feed as it is not known whether topically applied imiquimod is excreted in breast milk.

Overdosage: Persistent topical overdosing of imiquimod could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

Alternative Procedures: Patients may continue imiquimod for Grade 1 or tolerable Grade 2 toxicity without a dose reduction (graded according to NCI CTCAE v5.0). For intolerable Grade 2, Grade 3 or Grade 4 toxicity, imiquimod must be withheld until the toxicity has resolve to Grade 1 or tolerable Grade 2. At the discretion of the treating clinician, imiquimod may then be resumed as per following guidelines (Table 1). If an adverse event is not covered in the table, doses may be reduced or held at the discretion of the investigator for the subject's safety (eg, once every other day). The tables are intended to serve as guidance and cases in which the management is unclear should be discussed with the principal investigator or study medical monitor as appropriate.

Subjects with adverse events that are manageable with supportive therapy may not require dose reductions (e.g., local site irritation may be treated with non-medicating moisturizing gel rather than by dose reduction).

Subjects will be withdrawn from the study treatment if they fail to recover to Grade 0, Grade 1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related adverse event within 21 days unless the principal investigator agrees that the subject should remain on the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment.

Doses should not be increased during the 4 weeks of therapy.

Table 1. Dose Modifications

Dose Level	Dose
0	Apply once every day
-1	Apply once in two days
-2	Apply once in three days

2.3.2 KNOWN POTENTIAL BENEFITS

Topical application of imiquimod 5% cream may reduce the size of the tumor, so that less tissue will have to be removed at the time of surgery.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

While surgical excision is the first line treatment, imiquimod has been shown to be an efficacious, non-invasive topical treatment modality, especially when utilized in the neoadjuvant setting prior to initial surgery[31-34]. A topically applicable therapeutic agent has the advantage in that there is minimal systemic absorption, hence, it is well tolerated with negligible systemic adverse events[28].

3 OBJECTIVES AND ENDPOINTS

Type	Name	Time Frame	Brief Description
Primary	Clinical reduction in size of tumor, confirmed by reduction in tumor cell count	4-weeks compared to baseline	Change in tumor size measured at the endpoint compared to that of the baseline, histologically assessed by the change in proportion of tumor islands in the surgical tissue specimen, which is quantitatively confirmed by assessing tumor cell count using quantitative immunofluorescence, compared to that of the biopsy
Secondary	Safety and tolerability of topical imiquimod 5% cream	Continuously during the study and for 4-weeks after the last dose of treatment	Safety and toxicity will be assessed using CTCAE v5.0 criteria
Exploratory	Explore anti-tumoral and immunomodulatory effect of imiquimod	4-weeks compared to baseline	To evaluate the anti-tumoral and immunomodulatory effect of imiquimod using quantitative multiplex immunofluorescence

4 STUDY DESIGN

4.1 OVERALL DESIGN

We hypothesize that Imiquimod 5% topical cream applied daily on tumor for 28 days will significantly decrease the clinical tumor size with confirmation by histology. Minimal local and systemic adverse events are anticipated.

This is a single-arm, phase 0 exploratory study evaluating the efficacy of imiquimod 5% cream in early-stage oral cancer patients.

Study Intervention: All subjects will apply imiquimod 5% cream on the oral tumor and adjacent area, once a day before bedtime, for 28-days.

Schedule of Evaluations: Formal tumor measurements (length of longest dimension in cm) with photography will be performed and the baseline blood test result recorded. Safety assessment (documentation of side effects experienced by the participant) and tumor measurement will be performed at the midpoint visit. The safety assessment, including routine blood work and intra-oral clinical examinations, will be performed and the tumor size measured at the endpoint visit.

Response to treatment will be determined by formal tumor measurements with photography: Decrease in tumor size measured at the endpoint compared to that of the baseline, histologically assessed by the change in the proportion of tumor islands in the surgical tissue specimen, which is quantitatively confirmed by assessing tumor cell count using quantitative immunofluorescence in the surgical tissue specimen compared to that of the biopsy. Toxicity evaluation will utilize CTCAE v5.0 criteria.

Duration of Treatment: Subjects will continue treatment for a total of 28-days, until confirmed disease progression (defined as doubling of tumor size compared to baseline) or intolerable toxicity or side effects. Subjects will be withdrawn from the study and proceed with scheduled surgical excision.

Duration of Follow-Up: Toxicity will be graded using the NCI CTCAE v5.0 scoring system. Adverse events will be assessed continuously during the study and for 1 month after the last dose of treatment. Subjects will be followed for at least 1 month post-study, or until all treatment related adverse events have recovered to baseline or are deemed irreversible by the investigator. Subjects who are removed from study for reasons other than progression of disease will be followed every 3 months to evaluate disease status and survival analysis while the study remains open.

The current study is limited to assessing the endpoint response at the week 4 mark. However, lack of rapid tumor regression might not mean that the treatment was ineffective, and rapid early regression may be associated with no long-term benefits. Moreover, immune therapies often take longer than 4 weeks to work; therefore, clinical response may be underestimated with this duration. We will continue to follow the current cohort via periodic review of the electronic medical record beyond the R21 project term, and collect the recurrence and survival data to gain insight into the long-term effect of imiquimod.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is an exploratory single-arm study.

4.3 JUSTIFICATION FOR DOSE

The dosing schedule and treatment duration are not standardized[49]. The recommended schedule in the US and Europe is 5 times a week for 6 weeks with a success rate of 73–77%[32,50] – this is a total of 30 days of treatment, which is equivalent to 7 times a week for 4 weeks (a total of 28 days). Topical imiquimod was applied daily for 14 consecutive days intraorally without significant side effect, resulting in a complete resolution of recurrent OSCC[36]. Hence, a once a day for 4 weeks regimen of topical imiquimod closely follows the recommended schedule, with minimal adverse events and potentially optimal clinical response, without delay in surgical treatment.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed baseline, midpoint and endpoint visits, as well as the Day 60 follow-up phone call.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Biopsy confirmed primary oral squamous cell carcinoma (OSCC)
4. Clinical (TNM) stage I or II
5. Age >= 18 years
6. ECOG =< 2.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients currently on systemic or intraoral immunosuppressive therapy
2. Treatment with any other investigational agents for OSCC
3. HIV positive patients on combination antiretroviral therapy
4. Pregnant women are excluded from this study because imiquimod may have adverse effect on the fetus (FDA pregnancy risk category C). Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with imiquimod, breastfeeding should be discontinued if the mother is receiving study treatment
5. Male patients unwilling or unable to comply with pregnancy prevention measures
6. Subjects not receiving initial surgical treatment at MUSC.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Abstain from eating or drinking for at least 30 minutes after application of topical imiquimod cream.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure), tests with results that fail eligibility requirements may be repeated during the screening phase if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status (eg, after recovery from an infection).

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

A total of 15 patients will be enrolled to the study. Four patients already completed the study. The remaining 11 patients will be recruited at MUSC.

We will plan to accrue 3-5 patients per month. We anticipate that the last patient will be enrolled approximately 3-5 months after the study initiation at MUSC.

The MUSC Oral Biopsy Laboratory receives ~7000 specimens from the tristate area annually. Approximately 150-200 cases are of OSCC (oral squamous cell carcinoma). As these are biopsy specimens from the private dental practices, most of these OSCC are of early clinical stages. Once the histologic diagnosis of OSCC is rendered, the submitting clinician will be contacted by the PI, who is the case pathologist, for permission to directly speak with the patient. The patient will be informed of the clinical trial and referred to the MUSC Head and Neck Surgery for the initial consultation, at which time the medical history is reviewed and treatment option (surgery alone vs surgery with elective neck dissection) is discussed. If eligible, the patient will be approached to obtain consent. The surgeon will be informed of the patient's involvement in the clinical trial and the surgery will be scheduled for 4 week following the initiation of topical imiquimod therapy. Subjects will be limited to those who will receive surgical treatment at MUSC.

The protocol investigators will be available to all patients for further questions and information through a contact number provided on the consent form. During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patients during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes. Given considerable number of oral cancer cases received by the biopsy service, we do not anticipate difficulty in subject recruitment.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Topical imiquimod 5% cream is a TLR (Toll-like receptor) agonist. Imiquimod 5% cream is FDA approved for the topical treatment of the following.

- Clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratosis (AK) on the face and scalp in immunocompetent adults (1.1)
- Biopsy confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured (1.2).

- External genital and perianal warts/condyloma acuminate in patients 12 years old or older (1.3).

Because there is no FDA approved indication for the use in the OSCC patients, we will submit Investigatrional New Drug (IND) application for intra-oral use of drug in OSCC patients to the FDA.

Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben. Chemically, imiquimod is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of C14H16N4 and a molecular weight of 240.3.

6.1.2 DOSING AND ADMINISTRATION

Imiquimod is a topically-administered cream. Patients with adequate immune function will be started on a dose of 5mg once daily. Dosing will be adjusted for safety as delineated in Table 1. Treatment will consist of 28-day cycle. Treatment will continue for a maximum of 28-days or severe toxicity requiring cessation occurs.

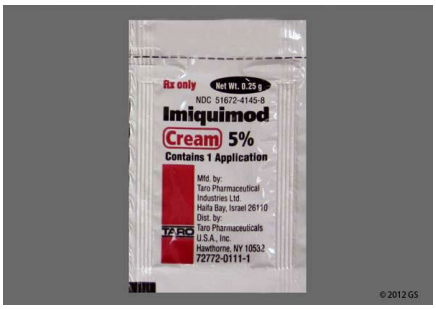
6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Twenty-eight packets (single-use packets) of imiquimod Cream, 5%, will be procured by the clinical research pharmacy and dispensed to the patient upon request by the PI/study team. The medication will either be overnighted via Fedex/UPS a day before Day 1 or delivered by career service to the patient's home address. Although imiquimod 5% topical cream has the 'external use only' label, it will be explained to the patients that it has been safely used in the vulvar, vaginal and cervical mucosa[34,55], as well as in the oral mucosa[36,54]. Patients are to return all unused medication to the investigator at the endpoint visit, which will then be returned to the research pharmacy for proper destruction and disposal.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Imiquimod cream (5%) are manufactured, packaged, and pre-labeled, which will be procured and dispensed by the clinical research pharmacy.



6.2.3 PRODUCT STORAGE AND STABILITY

The study drug will be stored in the research pharmacy in room-temperature.

6.2.4 PREPARATION

Not applicable.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

Subject compliance will be monitored with the aid of a "Patient Daily Diary" (Appendix B) which will be reviewed by the study team at each visit. Subjects who are non-compliant with protocol schedule or filling out the daily diary will be removed from the study at the discretion of the study investigator.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 RESCUE MEDICINE

Because there is a potential immunosupressive effect of concomitantly administered topical/systemic corticosteroids, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is using all types of corticosteroids. The topical therapies permitted will be non-medicating moisturizing gel and oral antihistamines for itching.

The use of rescue medications is allowable at any time during the study. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from topical imiquimod 5% cream does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). Patients who discontinue early (missing 14 or more days of daily treatment regimen) should return within 30 days of the last application of the study drugs for a follow up evaluation. Assessments including clinical oral examination and blood test may be performed at that time.

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for study treatment discontinuation
- Protocol specified endpoint assessment (clinical size of lesion, concomitant medication, daily diary form
- AE follow-up information: follow-up until resolution or determined by the investigator that the event has become stable or irreversible
- Survival data.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are enrolled in the study but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit 5 business days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Clinical size of tumor: For the purposes of this study, patients will be evaluated for response on Day 1, Day 14 and Day 29. Changes in OSCC size will be measured as the percent change from baseline compared to endpoint in the longest diameters will be reported for each patient.

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 5 days before the beginning of the treatment.

Histologic response: Pre- and post-treatment tumor tissue samples will be obtained from all 15 subjects as a part of standard of care. Pre-treatment tissue samples will be obtained from the diagnostic biopsy tissue. Post-treatment tissue samples will be obtained from the surgical resection tissue.

Timing of Biopsy Samples: The formalin-fixed, paraffin-embedded tissue samples will be obtained from the MUSC Oral Pathology & Pathology Department archived at the following time-points:

- Prior to treatment (anytime during the screening period) (mandatory)

- Post-treatment (immediately following the surgical resection) (mandatory)

Collection & Processing Instructions: Collection and processing of the tissue samples will be a part of standard of care. For the study, representative H&E slides of the biopsy and surgical specimen will be examined for correlation with clinical change in tumor size. The HCC Pathology Core laboratory will be notified by email (yoona@musc.edu) for retrieval of FFPE tissue blocks and generation of H&E slides and immunoblank slides. The email will contain the following information:

- Subject ID number
- Time point (e.g. baseline vs end of treatment)

The formalin-fixed, paraffin-embedded slides will first be stained with H&E for review and the representative tumor section slides will be selected by the board-certified pathologist (PI). The most representative area of the selected slides (one for biopsy and one for surgical tissue) will be macrodissected for further multispectral imaging (quantitative immunofluorescence). The slides will be stained with pan-cytokeratin using Lunaphore Comet automated stainers, and the pan-cytokeratin positive tumor cells for quantification of tumor cells present.

In addition, the percent change in the tumor cell proliferation marker (PCNA) and immune suppression marker on tumor cells (PD-L1) will be assessed using quantitative immunofluorescence.

Immunologic response: Immunoblanks will be delivered to HIMC in person for quantitative multiplex immunofluorescence study. The HIMC will also be notified by email on the day of immunoblank slide submission. The email will contain the following information:

- Subject ID
- Time point (e.g. baseline vs end of treatment)
- Contents of samples (number of immunoblank slides for each case)

The result will be reported as % change in the immune cell profiles.

8.2 SAFETY AND OTHER ASSESSMENTS

Adverse events will be monitored from the time of the first dose of imiquimod. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. All AEs (serious and non-serious) must be recorded on the source documents and eCRFs regardless of the assumption of a causal relationship with the study drug. All AEs of unknown etiology associated with imiquimod exposure should be evaluated to determine if it is possibly an irAE. Therapy-related AEs and the grade will be reported using the CTCAE v.5.0.To assess potential systemic AEs, Blood test to assess complete blood count (CBC) will be conducted prior to Day 1, and compared to that of the endpoint. The endpoint blood test result will be obtained from the patient's medical chart, which is performed as part of SOC prior to surgery.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The PI and study investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study team will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Not applicable

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 5-days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 5-days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials as required by an institution's written reporting procedures, the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 5-days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint: Imiquimod 5% topical cream applied daily on tumor for 28-days will decrease the clinical tumor size at least by 50% with confirmation by tumor cell count. Minimal local and systemic adverse events are anticipated.

- Secondary Efficacy Endpoint: Imiquimod will increase apoptosis and necrosis of the tumor cells and activate anti-tumoral immune cells.

9.2 SAMPLE SIZE DETERMINATION

In the only study available, which has one patient with recurrent oral squamous cell carcinoma (OSCC), imiquimod achieved a complete (100%) response with 14 days of daily treatment[43]. To be conservative, we will estimate the response rate (reduction in tumor size) to be at least 0.5 with 28 days of daily imiquimod treatment. In this proof-of-concept clinical trial, we can accrue and evaluate 15 subjects during the allotted 2-year study period. With 15 subjects and the estimate response rate of 0.5, we will achieve the 95% confidence interval (CI) of 0.239 to 0.761, using a two-sided exact binomial test with a type I error of 0.05. Because the trial is conducted between the diagnostic biopsy and the initial surgery, minimal loss to follow-up is anticipated. If the participants opts out of the trial during the 4-week period, we will accrual additional patients until we have 15 evaluable participants. Secondary toxicity analyses will include all patients who received the therapy.

9.3 POPULATIONS FOR ANALYSES

All patients treated in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Patients who initiate therapy but ultimately deemed unevaluable for response will be replaced with an additional patient to ensure that the required number of evaluable patients are accrued.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will estimate response rate of OSCC to topical imiquimod treatment and provide the exact 95% CI based on binomial distribution. Descriptive statistics will be used to quantify secondary end points of toxicity and tolerability. Statistical analyses will also be conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R (www.r-project.org), and $p<0.05$ (two sided) will be considered as statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

Clinical changes in tumor size will be measured as the percent change from baseline compared to endpoint in the longest diameters will be reported for each patient.
The pan-cytokeratin positive tumor cells will be quantified and the percent change will be calculated.

The concordance between the percent change in clinical size and the tumor count will be assessed using Cohen κ.

All of the patients who meet the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-9 will be considered to have a treatment failure (disease progression). Precise definitions for categories 4-9 will be protocol specific.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT / SAFETY ENDPOINT

Descriptive statistics will be used to quantify the secondary endpoints of toxicity and tolerability.

Summary of therapy-related adverse events and the grade will be reported using the CTCAE v.5.0.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Not applicable

9.4.5 PLANNED INTERIM ANALYSES

Not applicable

9.4.6 SUB-GROUP ANALYSES

All conclusions will be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals will also be provided.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be summarized and presented as the baseline characteristics.

9.4.8 EXPLORATORY ANALYSES

The precent change in immune profile following the imiquimod treatment (endpoint; surgical tissue) for each of 15 subjects will be compared to that of the baseline (biopsy tissue).

Paired t-test will be performed to assess the significance of the change in the marker expression levels. Statistical analyses will be conducted using SAS 9.4 (SAS Institute Inc.) and $p<0.05$ will be considered statistically significant.

In addition, the percent change in the tumor cell proliferation marker (PCNA) and immune suppression marker on tumor cells (PD-L1) will be assessed using quantitative immunofluorescence.

9.4.9 SURVIVAL ANALYSES

Using the time of data cutoff as Sep 30, 2023, the time from surgery (initial treatment) to the time to cancer recurrence (relapse-free survival) and death will be assessed.

The data will be shown as the
1. mean follow-up time in months
2. one year recurrence-free survival rate.

For the recurrence-free survival rate, the time-to-event efficacy will be estimated using two-sided corresponding 95% CIs.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: ECOG performance status criteria, Daily diary form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

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

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in

strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

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

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

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

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the HCC Data Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the HCC Data Repository, for use by other researchers including those outside of the study. Permission to transmit data to the HCC Data Repository will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the HCC Biosample Repository with the same goal as the sharing of data with the HCC Data Repository. These samples could be used to research the causes of oral cancer, its complications and other conditions for which individuals with oral cancer are at increased risk, and to improve treatment. The HCC will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the HCC.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	Medical Monitor
Angela Yoon, DDS	Name, degree, title
MUSC	Institution Name
173 Ashley Ave, BSB 344 MSC 507	Address
843-792-4495	Phone Number
yoona@mucs.edu	Email

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise in oncology, research pharmacy, research nursing, and data management. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the PI National Institutes of Health staff.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the HCC CTO's DSMC.
- On-site monitoring will be provided throughout the study with random review of certain data (less than 100% data verification or targeted data verification of endpoint, safety and other key data variables).
- CTO will be provided copies of monitoring reports within 10 days of visit.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits will be conducted by CTO's DSMC to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

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

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap, a 21 CFR Part 11-compliant data capture system provided by the CTO. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

[Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending

or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NCI Program Official and CTO. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers x years after the completion of the primary endpoint by contacting <specify person or awardee institution, or name of data repository>.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these

data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

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

10.2 ADDITIONAL CONSIDERATIONS

No additional considerations.

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
CTO	Clinical Trials Office
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HCC	Hollings Cancer Center
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
MUSC	Medical University of South Carolina
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
OSCC	Oral Squamous Cell Carcinoma
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
8	1/21/2022	Change of Institution	
9	8/30/2023	**Addition of tumor cell count quantification using immunofluorescence in the primary endpoint assessment** **Additional statistical analyses**	

11 REFERENCES

1. Sasahira T, Kirita T. Hallmarks of cancer-related newly prognostic factors of oral squamous cell carcinoma. Int J Mol Sci 2018;19:2413.
2. Kademani D. Oral cancer. Mayo Clin Proc 2007;82:878-887.
3. Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of Human Papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol 2015;33:3235-3242.
4. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002;52:195-215.
5. Markopoulos AK. Current aspects on oral squamous cell carcinoma. Open Dent J 2012;6:126-130.
6. Omura K. Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. Int J Clin Oncol 2014;19:423-430.
7. Cramer JD, Reddy A, Ferris RL, Duvvuri U, Samant S. Comparison of the seventh and eighth edition American Joint Committee on cancer oral cavity staging systems. Laryngoscope 2018;128:2351-2360.
8. Huang SH, O'Sullivan B. Overview of the 8th edition TNM classification for head and neck cancer. Curr Treat Options in Oncol 2017;18:40.
9. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:122-137.
10. Moeckelmann N, Ebrahimi A, Tou YK, et al. Prognostic implications of the 8th edition American Joint Committee on Cancer (AJCC) staging system in oral cavity squamous cell carcinoma. Oral Oncol 2018;85:82-86.
11. Tirelli G, Gatto A, Nata FB, et al. Prognosis of oral cancer: a comparison of the staging systems given in the 7th and 8th editions of the American Joint Committee on cancer staging manual. Br J Oral Maxillofac Surg 2018;56:8-13.
12. Faisal M, Bakar MA, Sarwar A, et al. Depth of invasion (DOI) as a predictor of cervical nodal metastasis and local recurrence in early stage squamous cell carcinoma of oral tongue (ESSCOT). PLoS ONE 2018;13:e0202632.
13. Almangush A, Makitie AA, Makinen LK, et al. Small oral tongue cancers (<4cm in diameter) with clinically negative neck: from the 7th to the 8th edition of the American Joint Committee on cancer. Virchows Archiv 2018;473:481-487.
14. Baykul T, Yilmaz HH, Aydin U, Aydin MA, Aksoy MC, Yildirim D. Early diagnosis of oral cancer. J Int Med Res 2010;38:737-749.
15. Yoon AJ, Wang S, Wang T, Kutler DI, LaRoche D, Philipone E, Peters SM, Hernandez B, McDowell BD, Stewart CR, Momen-Heravi F, Santella RM. MicroRNA-based risk scoring system to identify early-stage oral squamous cell carcinoma patients at high-risk for cancer-specific mortality. Head Neck 2020. doi.org/10.1002/hed.26089.
16. Amaravadi RK, Thompson CB. The roles of therapy-induced autophagy and necrosis in cancer treatment. Clin Cancer Res 2007;13:7271-7279.

17. Katayama M, Kawaguchi T, Berger MS, Pieper RO. DNA damaging agent-induced autophagy produces a cytoprotective adenosine triphosphate surge in malignant glioma cells. Cell Death Differ 2007;14:548–558.

18. Abedin MJ, Wang D, McDonnell MA, Lehmann U, Kelekar A. Autophagy delays apoptotic death in breast cancer cells following DNA damage. Cell Death Differ 2007;14:500–510.

19. Crighton D, Wilkinson S, O'Prey J, et al. DRAM, a p53-induced modulator of autophagy, is critical for apoptosis. Cell 2006;126:121–134.

20. Rose TL, Bonneau L, Der C, Marty-Mazars D, Marty F. Starvation-induced expression of autophagy-related genes in Arabidopsis. Biol Cell 2006;98:53–67.

21. Ahn MY, Kwon SM, Cheong HH, Park JH, Lee J, Min SK, Ahn SG, Yoon JH. Toll-like receptor 7 agonist, Imiquimod, inhibits oral squamous carcinoma cells through apoptosis and necrosis. J Oral Pathol Med 2012;41:540-546.

22. Smyth EC, Flavin M, Pulitzer MP, Gardner GJ, Costantino PD, Chi DS, Bogatch K, Chapman PB, Wolchok JD, Schwartz GK, Carvajal RD. Treatment of locally recurrent mucosal melanoma with topical imiquimod. J Clin Oncol 2011;29:e809-e811.

23. Schon MP, Schon M. Imiquimod: mode of action. British J Dermatol 2007;157:8-13.

24. Sohn KC, Li ZJ, Choi DK, Zhang T, Lim JW, Chang IK, Hur GM, Im M, Lee Y, Seo YJ, Lee JH, Kim CD. Imiquimod induces apoptosis of squamous cell carcinoma (SCC) cells via regulation of A20. 2014;9:e95337.

25. Stanley MA. Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. Clin Exp Dermatol 2002;27:571-577.

26. Geisse JK, Rich P, Pandya A, Gross K, Andres K, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. J Am Acad Dermatol 2002;47:390-398.

27. Stary G, Bangert C, Tauber M, Strohal R, Kopp T, et al. Tumoricidal activity of TLR7/8-activated inflammatory dendritic cells. J Exp Med 2007;204:1441-1451.

28. Bong AB, Bonnekoh B, Franke I, Schön M, Ulrich J, et al. Imiquimod, a topical immune response modifier, in the treatment of cutaneous metastases of malignant melanoma. Dermatology 2002;205:135-138.

29. Huang SJ, Hijnen D, Murphy GF, Kupper TS, Calarese AW, et al. Imiquimod enhances IFN-gamma production and effector function of T cells infiltrating human squamous cell carcinomas of the skin. J Invest Dermatol 2009;129:2676-2685.

30. Yokogawa M, Takaishi M, Nakajima K, Kamijima R, Digiovanni J, et al. Imiquimod attenuates the growth of UVB-Induced SCC in mice through Th1/Th17 cells. Mol Carcinog 2013;52:760-769.

31. Rich AM, Hussaini HM, Parachuru V, Seymour GJ. Toll-like receptors and cancer, particularly oral squamous cell carcinoma. Front Immunol 2014;5:464.

32. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: Results from a randomized vehicle-controlled phase III study in Europe. Br J Dermatol 2005;152:939-947.

33. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: A systematic review. Arch Dermatol 2009;145:1431-1438.

34. Iavazzo C, Pitsouni E, Athanasiou S, et al. Imiquimod for treatment of vulvar and vaginal intraepithelial neoplasia. Int J Gynaecol Obstet 2008;101:3-10.

35. Gkoulioni V, Eleftheriadou A, Yiotakis I, Ferekidou E, Chrisovergis A, Lazaris AC, et al. The efficacy of imiquimod on dysplastic lesions of the oral mucosa: an experimental model. Anticancer Res 2010;30:2891-2896.

36. Wester A, Eyler JT, Swan JW. Topical imiquimod for the palliative treatment of recurrent oral squamous cell carcinoma. JAAD Case Reports 2017;3:329-331.

37. Schmitz A, Duhoux F, Machiels JP. Window of opportunity studies: Do they fulfil our expectations? Cancer Treat Rev 2016;43:50-57.

38. Marous M, Bieche I, Paoletti X, Alt M, Razak AR, Stathis A. et al. Designs of preoperative biomarkers trials in oncology: a systemic review of the literature. Ann Oncol 2015;26:2419-2428.

39. Torezan LA, Festa-Neto C. Cutaneous field cancerization: clinical, histopathological and therapeutic aspects. An Bras Dermatol 2013;88:775-786.

40. Christensen SR. Recent advances in field cancerization and management of multiple cutaneous squamous cell carcinomas. 2018;7: doi: 10.12688/f1000research.12837.1.

41. Wang B, Zhang S, Yue K, Wang XD. The recurrence and survival of oral squamous cell carcinoma: a report of 275 cases. Chin J Cancer 2013;32:614-618.

42. Gombos K, Horvath R, Szele E, et al. miRNA expression profiles of oral squamous cell carcinomas. Anticancer Res 2013;33:1511-1517.

43. Troiano G, Mastrangelo F, Caponio VCA, et al. Predictive prognostic value of tissue-based microRNA expression in oral squamous cell carcinoma: a systemic review and meta-analysis. J Dent Res 2018;97:759-766.

44. Sarode GS, Sarode SC, Maniyar N, Anand R, Patil S. Oral cancer database: a comprehensive review. J Oral Pathol Med 2018;47:547-556.

45. Kumarasamy C, Madjav MR, Sabarimurugan S, et al. Prognostic value of miRNAs in head and neck cancers: a comprehensive systemic and meta-analysis. Cells 2019;8. doi: 10.3390/cells8080772.

46. Megill C, Wilkin T. Topical therapies for the treatment of anal high-grade squamous intraepithelial lesions. Semin colon Rectal Surg. 2017;28:86-90.

47. Daayana S, Elkord E, Winters U, Pawita M, Roden R, Stern PL, Kitchener HC. Phase II trial of imiquimod and HPV therapeutic vaccination in patients with vulvar intraepithelial neoplasia. Br J Cancer 2010;102:1129-1136.

48. Tristram A, Hurt CN, Madden T, et al. Activity, safety, and feasibility of cidofovir and imiquimod for treatment of vulval intraepithelial neoplasia (RT^3VIN): a multicenter, open-label, randomized, phase 2 trial. Lancet Oncol 2014;15:1361-1368.

49. Singal A, Daulatabad D, Pandhi D, Arora VK. Facial basal cell carcinoma treated with topical 5% imiquimod cream with dermoscopic evaluation. J Cutan Aesthet Surg 2016;9:122-125.

50. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: Results from two phase III, randomized, vehicle-controlled studies. J Am Acad Dermatol 2004;50:722-33.

51. Gartrell RD, Marks DK, Hart TD, Li G, Davari DR, Wu A, Blake Z, Lu Y, Askin KN, et al. Quantitative analysis of immune infiltrates in primary melanoma. Cancer Immunol Res 2018;6:481-493.

52. Parra ER, Uraoka N, Jiang M, Cook P, Gibbons D, Forget MA, et al. Validation of multiplex immunofluorescence panels using multispectral microscopy for immune-profiling of formalin-fixed and paraffin-embedded human tumor tissues. Sci Rep 2017;17:13380.

53. Koyama T, Chen H. "Proper Inference from Simon's Two-Stage Designs." Statistics in Medicine 2008;27(16), 3145–3154.

54. Mane S, Patilsoman B, Bhate P, Das D, Malusare P, Tomar N. To evaluate the efficacy and tolerability of topical 5% imiquimod in cases of oral leukoplakia: a pilot study. J Indian Acad Oral Med Rad 2021;33:27-31. *https://www.jiaomr.in/text.asp?2021/33/1/27/312195*

55. Pachman DR, Barton DL, Clayton AH, et al. Randomized clinical trial of imiquimod: an adjunct to treating cervical dysplasia. Am J Obstet Gynecol 2012;206:e1-42. doi: 10.1016/j.ajog.2011.06.105

APPENDIX A: **ECOG PERFORMANCE STATUS CRITERIA.**

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: DAILY DIARY

Exploratory clinical trial of topical Imiquimod 5% cream as window-of-opportunity monotherapy for early-stage oral cancer

Patient Name: _____ Study ID: _____ MRN:_____

(To be Completed by RN)

Total Daily Dose of Imiquimod: 5mg

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.

SPECIAL INSTRUCTIONS

1. Imiquimod 5% cream should be applied once a day at bedtime.
2. Missed doses should be skipped and not taken as a double dose at the next dosing time.
3. Imiquimod 5% cream should be **stored at room temperature**.

Day	Medication	Date	Time	Comments
Example	Imiquimod	5/1/2021	9:00PM	
1	Imiquimod			
2	Imiquimod			
3	Imiquimod			
4	Imiquimod			
5	Imiquimod			
6	Imiquimod			
7	Imiquimod			
8	Imiquimod			
9	Imiquimod			
10	Imiquimod			
11	Imiquimod			
12	Imiquimod			
13	Imiquimod			
14	Imiquimod			
15	Imiquimod			
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23	Imiquimod			
24	Imiquimod			
25	Imiquimod			
26	Imiquimod			
27	Imiquimod			
28	Imiquimod			

Patient Signature: _____ Date: _____

Consenting Professional/Research RN Signature: _____ Date: _____

Consenting Professional/Research RN Comments:

_____

_____

_____