Statistical Analysis Plan (SAP)

The Safety and Efficacy of topical 2% Lovastatin/2% Cholesterol and topical 2% Lovastatin for the treatment of Disseminated Superficial Actinic Porokeratosis: A single-blinded randomized clinical trial

Principal Investigator Dirk Elston, MD, Professor and Chairman of Department of Dermatology and Dermatologic Surgery
Medical University of South Carolina
Charleston, SC

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Author Alex Drohan, MD
Department of Dermatology and Dermatologic Surgery
Medical University of South Carolina, Charleston, South Carolina

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Principal Investigator	Dirk Elston, MD
Signature:	
Date:	1/12/22

Author	Alex Drohan, MD
Signature:	Alex Drohan
Date:	1/12/2022

Abbreviations

DSAP	Disseminated Superficial Actinic Porokeratosis
GASI	General Assessment Severity Index
ITT	Intention to Treat
PP	Per Protocol

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1 Introduction

The aim of this study is to test in a single-center randomized clinical trial, if topical statins combined with topical cholesterol can reduce the severity (size, color, quality of life impact) of disseminated superficial actinic vs statin therapy alone.

This statistical analysis plan (SAP) will give more detailed descriptions of the endpoints in the study and the corresponding analysis.

2 Study Design

Patients with previous diagnosis of DSAP will be approached for informed consent as directed in sections 8.0 and 9.0 of the protocol. If the patient is eligible for the study, he or she will be randomly assigned to one of two groups, Group A (cholesterol/lovastatin) and Group B (lovastatin only). The patient will not be informed of which group they are in and will not be informed of what their study medication is, allowing single-blinding. Researchers will not be masked.

Enrolled subjects will be followed up at monthly intervals for three months via virtual check-in using an MUSC approved HIPAA compliant technology. At each visit, participants will undergo brief, limited physical examination (in order to determine disease severity and affected body surface area); additionally, clinical photographs of the lesion will be obtained in clinic or shared virtually with the investigators via secure email (sent to MUSC Outlook email). The physical exam will occur in-person or by using the virtual visit technology, which allows us to see the patient and visualize their skin findings. Photographs will be stored in the coded study-specific medical record for further analysis of lesion features.

At each visit a Patient Quality of Life, Physician Global Assessment Scale, and RAND36 will be administered.

Patients will be contacted via formal virtual visits at weeks 4, 8, and 12 and non-formal check-ins at weeks 2 and 6. Patients will be asked about compliance and any adverse effects experienced. Patients are also encouraged to contact Alan Snyder and/or Gabriella Santa Lucia at any given point during the study if they think they are experiencing study-related side effects. Immediate consultation will follow to determine the severity of such event and necessary impacts on patient health and participation. Non-formal check-ins will be done over phone by study team member to assess for any adverse effects at weeks 2 and 6 of treatment.

Compounded topical medication prescribed to subjects will be self-applied twice daily. These medications will be prepared by Tidewater Pharmacy in Mount Pleasant, SC or Chemistry Rx in Philidelphia, PA dependent upon patient geography. They will be prepared so the study will remain single-blinded (only investigators know which study drug they are receiving) and associated costs will not be covered by the research budget. The cost of the medication will be approximately $85 when dispensed by Tidewater Pharmacy,

or $110 when dispensed by Chemistry Rx. The differences in costs are attributed to shipping and pharmacy fees.

Both pharmacies will be compounding the drugs to be used in this study, and the compounding formula (recipe) will be identical between these two compounding pharmacies.

Enrollment and prescription drug delivery to other states will not be performed until the respective state pharmacy boards confirm the legality of clinical telehealth interventions and out-of-state pharmacy prescriptions. All state and federal guidelines will be followed according to their regulations and recommendations.

Patient prescriptions will be called in to their respective pharmacies by credentialed study team members after enrollment is completed. Individual prescriptions will be called in to the aforementioned pharmacies so that the pharmacies can individually ship the medication to the respective participant. Both pharmacies are well aware of the study protocol and procedures for sending the prescription. This will occur by standard procedure of calling medications for patients:

1. The study team member will call the pharmacist to inform them that a participant has been enrolled and ready to receive one of the two single-blinded drugs. On the prescription label there will be a codename, application instructions, and storage instructions.

2. Per standard procedure of calling in a prescription, the study team member will verbally inform the Tidewater/Chemistry Rx pharmacist of the patient name, birthday, and phone number so that the medication can be prescribed and so that the patient can be contacted by the pharmacist for shipping and payment purposes.

3. The pharmacist will contact the patient over the phone in order to complete the medication payment over the phone and to identify the address to which the medication will be sent to.

4. The subject will inform the study team member upon receival of the medication, confirm that they received the correct, randomized medication.

5. All of the information related to drug disposal and reception will be recorded on the coded Drug Accountability Sheet, which is located separately in the secure box drive.

Medications will be able to be shipped to all continental US states by Chemistry Rx, except Alabama. This is because Chemistry Rx does not have the license to dispense to Alabama. Therefore, any participant reliant upon an Alabama address to receive their medication will not be allowed to participate in this study.

Dermoscopic and clinical photographs will be subsequently analyzed for the presence of cornoid lamella. The team will record any additional dermoscopic or clinicals feature that may arise during the analyses.

Frequency of dermoscopic and clinical features will be analyzed against clinical involution to find possible predictors.

Procedures during the day of imaging:

The doctor will identify the lesion(s) that will be analyzed.

The lesion(s) will be measured and clinical and dermoscopy photographs will be taken. Facial images might be taken to assess lesions on the head area.

Schedule of events:

Event	Screening Baseline Visit 1	Week 4 (virtual)	Week 8 (virtual)	Week 12 (virtual)
Informed consent	X			
Eligibility Assessment	X			
Demographics	X			
Physical Examination	X			
Clinical photograph & Scale (3x) administration	X	X	X	X
Dermoscopic photograph	X			
Adverse events monitoring	X	X	X	X

2.1 Sample Size Calculation

DSAP is a rare disease that effects people from a wide geographical region. The goal sample size for the study was to recruit 50 subjects, however, due to recruiting limitations and state regulations, we were only able to enroll 31 patients. No formal sample size calculation was necessary as this study is first of its kind.

3. Aims and Objectives

- The purpose of this study is to evaluate the effectiveness of cholesterol/lovastatin versus lovastatin alone to treat porokeratosis. Our working hypothesis is that both topical cholesterol/lovastatin and lovastatin alone are helpful in treating patients with disseminated superficial actinic porokeratosis (DSAP).
- Aims:
  - 1. To evaluate the response (lesion size, color, patient quality of life) to treatment with topical cholesterol/lovastatin and lovastatin alone in a series of patients with the diagnosis of DSAP.
  - 2. To characterize lesion patterns following topical treatment and patterns of lesion regression.
  - 3. Access quality of life outcomes through RAND36 and DLQI surveys.

4. Outcomes

This section will present the outcomes investigated to answer the study aims and objectives. The analyses are described in section 6 Analyses.

4.1 Primary outcome

Percentage of lesion clearance after 12 weeks of therapy using an exploratory clinical measure modified from a validated psoriasis index. The Disseminated Actinic Porokeratosis General Assessment Severity Index (DSAP-GASI) included plaque/rim elevation, scaling, and color (0= clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe).

4.2 Secondary outcomes

Self-reported evaluations (better, unchanged, worse) on overall appearance, color, scale, pain, and itch. Application frequency and consistency along with safety and tolerability were also assessed at each visit.

Surveys: Patient quality of life measures, DLQI,and RAND36

4.3 Safety Outcomes

Adverse events

Adverse events are reported at each clinic visit. Patients are also encouraged to contact Alan Snyder and/or Gabriella Santa Lucia at any given point during the study if they think they are experiencing study-related side effects. Immediate consultation will follow to determine the severity of such event and necessary impacts on patient health and participation. Participants will also be contacted by phone by study team member to assess for any adverse effects at weeks 2 and 6 of treatment.

5. Populations and subgroups to be analyzed

5.1 Populations

Intention-to-treat (ITT)

All randomized study subjects.

Per Protocol (PP)

All randomized study subjects completing the whole study period (complete cases). For a specific analysis, study subjects with missing data on any of the variables in the model will be excluded from the analysis. Analyses of this population is seen as a sensitivity analysis to investigate whether conclusions are sensitive to assumptions regarding the pattern of missing data.

6. Analysis

All enrolled subjects are considered in the demographic data and safety analysis. Treatment efficacy is based on investigator-standardized patient-documented photographs. Repeat photo documentation will be obtained if image quality was inadequate or angle, lighting or location is not standardized to prior photos.

6.1 Primary outcome

The primary analysis will compare the improvement in DSAP-GASI scores before treatment and after treatment in both groups. Only participants with clearly documented photos across all visits will be considered for the DSAP-GASI efficacy analysis. The scores will be graded by two blinded, trained physicians. Cronbach's Interrater reliability will be calculated among raters across visits and the scores will be averaged for each of the four visits. Overall efficacy will be examined using a 2X4 (Drug X Time) Repeated Measures Analyses of Variance (ANOVA). The statin/cholesterol vs statin groups will be compared and evaluated for significant differences

6.2 Secondary Outcomes

Self-reported patient satisfaction on overall appearance, size, and color, will be recorded and examined using Chi-Square across drug for the final visit. Application frequency and safety may also be evaluated.

A cross-sectional analysis of sociodemographic data and self-reported DSAP-related impact on QoL (scale 1-10) was averaged at baseline, while the RAND36 and Dermatology Life Quality Index (DLQI) were distributed and averaged at weeks 0, 4, 8, and 12. Statistical measures used in analysis included a Repeated Measures Analyses of Variance (ANOVA) and Pearson correlation coefficient.

7. Missing Data

Patients who failed to submit photographs for the analysis will be removed from the DSAP-GASI efficacy analysis. Missing data will be recorded and excluded from analysis.