Novel Strategies for Reducing Burn Scar Itch

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:*

Signed: _____ Date: _____

Name
Title

1.0 Background

Every year more than one million people in the United States are burned, and ~480,000 cases receive direct medical intervention.[1, 2] The cost is high both financially and personally to the survivor. The annual cost of treating burns in the U.S. is estimated to exceed ten billion dollars.[3] With improved burn treatment extending the lives of those whose injuries were previously fatal, strategies to reduce the impact of itch from scar on physical and psychosocial outcomes and health-related quality of life are a priority for survivors and clinicians.[4-8] Of the patients who survive being burned, 60 to 90% (288,000 to 900,000 individuals each year) will develop hypertrophic scars.[3, 9, 10] These scars restrict movement, itch, and are painful. Burn scars also severely limit participation in everyday activities (e.g., work, school, play, self-care), cause unhappiness with appearance, and interfere with sleep even decades after injury.[9, 11, 12] As a result, quality of life is negatively affected.[9, 11-15] The impact of hypertrophic scar on psychosocial outcomes is great[16-18]; survivors report depression, significant dissatisfaction with their appearance, reduced health-related quality of life, and decreased social interactions.[9, 11-15, 19-25] Social isolation is not uncommon, which in the general population has been linked to greater depression and disability later in life.[26-28] We and others described decreased quality of life from scarring in pediatric and adult burn patients.[14, 15] Progress toward prevention or attenuation of hypertrophic scar has been slow; despite identifying risk factors for contracture / hypertrophic scar formation,[11, 12, 29, 30] long-term reduction in hypertrophic scar and the associated sequelae such as itch is modest, even when accompanied by surgical scar revision, massage, pressure therapies, steroids, and silicone dressings to try and reduce scar formation.[10]

Itch is one of the leading pervasive problems identified by burn patients and care providers.[31-35 9, 13, 15, 36-40] This itch interferes with sleep, concentration during work or school, and activities (e.g. sports, exercise). Despite trials of many agents, there is a dearth of effective therapies; as a result, treatment of burn-induced itch has not progressed much over the past decade. Available therapies, mainly H1 antihistamines (diphenhydramine and hydroxyzine) and gabapentin, are utilized but are not prescribed consistently and as a result are of limited efficacy. Even more than 10 years after a burn, 58% of surveyed survivors report itch as problematic. Survivors describing the interminable itch report sleep disruption, reduced participation in daily activities, and reopening of the wound or scar while scratching. Other strategies for reducing itch, including H2 antihistamines and mast cell stabilizers, have been demonstrated to be effective in other patient populations. These therapies have increased efficacy when used in combination with each other (providing H1 and H2 antihistamines alongside application of a topical mast cell stabilizer), however, they have not been tried in burn patients suffering from itch. Here we will test the oral administration of the H2 antihistamine famotidine (20mg) with topical application of the mast cell stabilizer cromolyn sodium (4%).

2.0 Rationale and Specific Aims

For this clinical trial, we will compare placebo (capsule without drug and lotion without drug) to famotidine (H2 antihistamine) and cromolyn sodium (a mast cell stabilizer). Our study will determine whether itch can be significantly decreased in burn survivors randomized to this therapy. This study will demonstrate whether a multimodal approach to burn scar itch management is beneficial per patient reported outcomes measures (PROMS) and clinical evaluations. This therapeutic approach is a significant departure from the current care provided to burn survivors.

In this single center study, adult burn survivors reporting itch due to scar (n=44) will be randomized to Placebo (n=22; recommended treatment with an H1 antihistamine, administration of placebo capsule and lotion) or PLUS (PLUS: n=22; H1 antihistamine recommended plus famotidine and 4% topical cromolyn sodium). Participants will utilize these therapies twice daily for 3 months from the time of enrollment. At study start and again at 3 months, assessments of physical and functional outcomes will be performed. The primary outcome is the patient's evaluation of itch, as measured with the Visual Analog Scale. Secondary outcomes include scar severity (Patient and Observer Scar Assessment Scale, and objective measurements of surface area, volume, blood flow, color, height, hardness, reopened area), activity (Fitbit); quality of life (Brisbane Burn Scar Impact Profile, PROMIS-29); pain (VAS pain); and patient perception of change in itch 3 months after initiating treatment and again 3 months after completion of study protocol (Patient's Global Impression of Change).

We will test a combination of H1 antihistamine, H2 antihistamine, and a mast cell stabilizer to determine whether itch is significantly reduced with this protocol, laying the groundwork for a larger future clinical trial, with the ultimate goal of improving adult survivor of burn outcomes (itch, scar severity, quality of life, activity).

Study aims: Our goal is to demonstrate that a multi-modal approach to treating burn scar itch improves outcomes important to burn survivors: decreasing itch, improving scar quality/reducing severity, increasing activity, and better quality of life.

We will accomplish this with the following *Specific Aims:*
Specific Aim 1: Determine the effect of treatment on itch.
Specific Aim 2: Determine the effect of treatment on scar severity.
Specific Aim 3: Determine whether treatment changed activity measured by Fitbit and patient report.
Specific Aim 4: Determine the effect of treatment on quality of life and patient impression of change.

Specific Aim: 5. Determine the influence of skin microbiome on itch.

Assessments and techniques that may be used:

- Visual analog scale for itch
- Visual analog scale for pain
- Patient and observer evaluation of the scar (Patient and Observer Scar Assessment Scale v3.0)
- 3-dimensional photography for contracture area and volume
- Physical properties of the wound / scar / contracture measured with the DermaLab Combo: trans epidermal water loss, elasticity, temperature, scar thickness, color
- Blood flow (laser speckle analysis)
- Fitbit activity tracker
- Quality of life / well-being / performance of activities using the Brisbane Burn Scar Impact Profile and PROMIS-29 instruments
- Patient's Global Impression of Change
- Skin microbiome collection

3.0 Inclusion/Exclusion Criteria

Participants must meet all the inclusion criteria in order to be eligible to participate in the study. Inclusion criteria are:

- Participant has provided informed consent in a manner approved by the IRB and is willing and able to comply with the trial procedures.
- Adults: ≥18 to <80 years of age.
- Has an itchy burn scar at least 10 square centimeters or larger, and at least 10cm from an open wound.

Participants meeting any of the exclusion criteria at baseline will be excluded from study participation.

Exclusion criteria are:

- Failure to obtain consent or unable to return for follow up assessments.
- Patient is unable to follow the protocol required assessments.
- Member of a vulnerable class (e.g., prisoners, pregnant participant, etc.).
- Any medical history of chronic kidney disease.
- Any medical condition that, in the opinion of the investigator or physician, would place the participant at increased risk for participation.
- Women who are breastfeeding.
- Concurrent participation in another interventional clinical trial (to avoid confounding factors that may influence outcomes).
- History of prior non-compliance or the presence or history of psychiatric condition (including drug or alcohol addiction) that would, in the opinion of the investigator, make it difficult for the participant to comply with the study procedures or follow the investigators instructions.
- Age < 18 or ≥ 80 years.
- Taking one of the following medications: cefditoren, dasatinib, delavirdine, fosamprenavir, atazanavir, erlotinib, ketoconazole, itraconazole, ledipasvir/sofosbuvir, nilotinib, rilpivirine, cefuroxime, neratinib, pazopanib, risedronate, or tizanidine.
- Has a pre-existing inflammatory or itchy skin disease.
- Is taking an H2 antihistamine for another indication.

4.0 Treatment Assignment/Randomization

Consented patients will be randomized to either 1) Placebo (recommended active H1 antihistamine, plus placebo famotidine and placebo cromolyn sodium) or
2) PLUS (recommended active H1 antihistamine, plus active famotidine and active cromolyn sodium) by using block randomization (performed by Dr. Spratt). The randomization schedule will be sent and stored only with members of the Investigational Pharmacy and 1 member from the Research Coordinator Support Services (Research Nurse Manager) to confirm drug accountability.

5.0 Study Procedures

Summary: Patients reporting an itchy burn scar will be approached for enrollment by their treating physician, who may be a co-investigator of this study; we intend to enroll 44 patients. Participants will then be consented, enrolled, randomized, and assigned a study ID by RCSS clinical coordinator/nurse pool personnel, who will also schedule study visits, communicate with participants, and assist the clinician investigators with data collection in

the clinic. Block randomization will be used to allocate patients to either the SoC or SoC-PLUS group.
Participants will remain on their current medications while in the study. All participants will receive the standard of care, which is a recommendation to take the oral H1 antihistamine diphenhydramine (Benadryl). Participants will be asked to record their diphenhydramine intake in their log book.

Administration of study medications: twice daily for 3 months. Patients will be instructed to take a capsule containing placebo or 20mg famotidine twice daily, and to use the lotion (placebo or 4% cromolyn sodium) twice daily.

The first assessment will be performed at the time of enrollment to obtain baseline measurements and photos, and patients will be given instructions for medication administration. When patients return to clinic about 3 months (±15 days) after enrollment, the outcomes listed below will be assessed. Participants will complete the study 6 months (±15 days) after starting study medication. This 6-month visit will be completed by a phone call. The study coordinator will call participants at a time and date convenient for both parties. The coordinator will ask the participant the questions on the PGIC and VAS Itch and Pain questionnaires.

Event	**Timing**	**Included procedures**	**Included patients**
Consent & randomization	At enrollment		All
Data collection from EMR	Throughout study		All
Medication Administration	Twice daily for 3 months	Call to patient to check on compliance	All
Itch measurement	At study start, weekly for 3 months, at 3 and 6 months (+/- 15 days each timepoint) after start of study	Visual analog scale Itch (VAS Itch), monthly call to remind patient to record medication use and itch evaluation in logbook	All
Measurements	At study start, and at clinic visit approximately 3 months after study start (±15 days)	Photographs, Physical properties of the scar, Blood flow, Questionnaires (POSAS, BBSIP, PROMIS-29, PGIC, VAS Pain)	All
Sample Collection	At study start, at 3 and 6 months after study start (±15 days each timepoint). 6 month swab collection will be optional.	Skin Swab Collection	All
Fitbit Sync	Month 1, 2, 3 (+15 days, each timepoint)	Call to patient to remind to sync Fitbit data on app.	All

Post-study questionnaires	6 months (± 15 days) after study start (end of the study)	Questionnaires (PGIC and VAS Itch and Pain)	All

	Pre-study	Study Start	Twice Daily for 3 months	Weekly for 3 months	~1 month (+/- 15 days)	~2 months (+/- 15 days)	~3 months (+/- 15 days)	~6 months (+/- 15 days)
Informed consent	X							
Randomization		X						
Demographics		X						
Study Staff Medication Administration		X						
Participant Medication Administration and Logbook			X					
Physical Exam (clinical visit)		X					X	
Visual Analog Scale (VAS itch)		X		X			X	X[1]
3D photography		X					X	
Questionnaires (POSAS, BBSIP, PROMIS-29, PGIC, VAS Pain)		X					X	
DermaLab Combo		X					X	
Laser Doppler		X					X	
Skin microbiome collection		X					X	X[2]
Fitbit Sync					X[1]	X[1]	X	X[1]
Post-study Questionnaires (PGIC and VAS Itch and Pain)								X[1]

1. Completed virtually by phone call.
2. Optional.

Consent Procedures

A partial waiver of consent will be obtained for screening purposes. This protocol will use the following recruitment methods to try to identify potential participants for this trial: Epic SlicerDicer, Epic MyChart recruitment, and direct in-office recruitment. If in-office recruitment is utilized, a treating physician will approach the patients identified through screening to inquire whether they would like to learn about the research study. Patients answering in the affirmative will then be approached by study staff to discuss the study. This discussion will take place in a private room and the patient will be informed that their participation is voluntary and their choice to participate or not will not affect their medical care. All conversations will take place by qualified study staff in the patient/caretaker's native language (Spanish or English).

If Epic SlicerDicer is utilized, the originally de-identified information of potential participants will be re-identified. After re-identification, the potential participant's medical record will then be reviewed for eligibility. If eligibility criteria are met, then the procedures for in-office recruitment will be followed.

If Epic MyChart recruitment is utilized, a MyChart recruitment message will be sent to patients who have consented to be contacted for opportunities to participate in research studies, who have had a history of a burn. The patient-facing study name and description for the MyChart recruitment message will be submitted for UTMB IRB approval. If the potential participant responds to the study coordinator that they would like to receive information about the study, the study coordinator will contact the potential participant via normal means (phone, email, office visit, etc.).

After the study information has been provided to the participant and fully explained and it is felt that the participant understands the implications of participating, the IRB-approved written informed consent form shall be signed and dated by the participant and the individual obtaining consent. The participant shall be given a copy of the signed informed consent form; the original shall be kept with the participant's study records. Documentation of informed consent will be in accordance with IRB policy.

Qualifying patients who agree to participate will be consented, enrolled, and randomized by study personnel. Written informed consent will be obtained from all participants before any study related procedures are performed; screening records will be maintained so that reasons for not enrolling in the study can be evaluated to determine barriers to participation.

Spanish Speaking Participants

For Spanish speaking participants, a certified Spanish Medical Interpreter will be utilized. The Spanish Medical Interpreter must be certified from 1 of the following 4 UTMB IRB approved options:

1. UTMB Language Services (https://intranet.utmb.edu/las/bsaprogram)
2. American Translator Association (www.atanet.org)
3. National Association of Judiciary Interpreters and Translators (https://najit.org)
4. National Board of Certification for Medical Interpreters (www.certifiedmedicalinterpreters.org)

Participants will be randomized to Placebo (recommending treatment with an oral H1 antihistamine) or PLUS (PLUS: recommending an oral H1 antihistamine plus famotidine and topical cromolyn sodium). A total of 44 participants will be randomized to either SoC (n=22) or SoC PLUS famotidine and cromolyn sodium (n=22). Drug administration for 3 months will be masked (to patients, their families, and staff conducting assessments or data analysis) by packaging into non-identifying capsules or similar lotion container.

The first assessment will be performed at the time of enrollment to obtain baseline data. All enrolled participants will be followed on an intent to treat basis with assessments of physical, functional, and outcomes data [Questionnaires (visual analog scale (VAS pain and VAS itch), Patient and Observer Scar Assessment Scale (POSAS), Brisbane Burn Scar Impact Profile (BBSIP), Patient reported outcomes measurements information system 29 (PROMIS-29), patient's global impression of change (PGIC)); Objective measures (surface area, volume, blood flow, color, height, hardness, reopened area); Activity assessed by

Fitbit; Study Medication review to monitor compliance] and [skin microbiome collection] collected at time of enrollment and 3-months after that. Only the PGIC, VAS itch, and VAS pain will be administered at 6 months. For the return to clinic visit at ~ 3 months after study start, the assessment window will be ± 15 days (e.g., 3 months ± 15 days). Participants will complete the study about 6 months after discharge (+/- 15 days).

All assessments at enrollment and 3 months later will be performed in person at UTMB; if patients are unable to return to clinic, questionnaires will be administered via phone, Microsoft Teams, email, or mail, and physiological assessments will be performed via phone or Microsoft Teams interview for demographics and intercurrent illness. Due to the safety profile of the selected therapies, adverse effects (AEs) are not anticipated, but treating physicians will report any AEs to the MPIs (Dr. Wolf or Dr. Finnerty) as required by severity and institutional / funder requirements, who will escalate to the IRB and/or DSMB as required. Investigators involved in data analyses will remain masked until the statistician codes the list of variables to be analyzed.

Additionally, an activity monitor (Fitbit Zip) will be issued to all participants after enrollment. This model provides physical activity measurements such as activity counts, energy expenditure, steps taken, distance travelled, and activity intensity levels. The application to the Fitbit will be downloaded onto the participant's preferred device after enrollment by study staff. An email account will be set up for the participant by the investigator or delegated study staff. This email account will only be accessible to the study staff, not the participant, in order to retrieve the data from the Fitbit. Only the participant's height, weight, sex, and age will be entered. If a name or date of birth is requested, a randomly generated "dummy" entry will be provided. The participant will be reminded to sync device data with the application at every in-clinic visit or via telephone call by study staff (months 1, 2, and 3) to ensure no data is lost due to lack of syncing device with application. The activity monitor for estimation of daily activity should be attached to the participant's clothing in a location that is comfortable to them. It should be always worn, including when sleeping. The activity monitors are water resistant, not waterproof, and can be disinfected with hospital grade solution/spray. The participant will not be required to return the Fitbit when they complete the study.

Standard burn scar care will be in accordance with the standard of care, including but not limited to treatments such as massage, pressure garments (interim and custom manufactured), wraps, topical moisturizers, and silicon scar sheets. At each visit, participant use of these treatments will be recorded.

Participants will be followed for about 6 months (+/- 15 days) following enrollment. This will allow for determination of any potential long-term benefits or side effects of treatment or treatment cessation.

Data analysts will not be privy to randomization information.

<u>Data to be collected (unless otherwise indicated, performed at baseline, and about 3 months after enrollment).</u>
The investigators, or delegated study staff, will collect participant data on the case report forms, logbook, or survey instruments and enter the data into a trial spreadsheet; electronic data files may be captured from productivity / habit tracking software from the Fitbit app.

- Baseline patient information data (age, sex, comorbidities) [source: EMR]
- Injury characteristics (size of burn: total TBSA and full thickness TBSA; burn location)

[source: EMR]

- Photographs (2D standard light and distance; 3D for calculating wound/contracture size and volume) [source: research measurement]
- Current scar treatments [source: EMR]
- Logbook (entries regarding medication use and VAS) [source: logbook for research]
- Visual analog scale for itch [source: research measurement]
- Visual analog scale for pain [source: research measurement]
- Patient and observer evaluation of the scar (Patient and Observer Scar Assessment Scale v2.0) [source: research measurement]
- Physical properties of the wound / scar / contracture measured with the DermaLab Combo: trans epidermal water loss, elasticity, temperature, scar thickness, color [source: research measurement]
- Blood flow (laser speckle analysis) [source: research measurement]
- Fitbit activity tracker [research measurement]
- Skin Microbiome Collection [research measurement]
- Quality of life / well-being / performance of activities using the Brisbane Burn Scar Impact Profile [24], and PROMIS 29.
- Patients will also be asked to evaluate the effect of treatment using the Patient's Global Impression of Change and to rate their itch and pain with the visual analog scale. ~ 3 and 6 months following enrollment. [source: research procedure]

Compensation will be $100 to be provided after each in-person completed visit time point (study start and 3 months), and $20 for the virtual 6-month visit for a total of $220 provided to each participant and will be made in the form of credit on a UTMB ClinCard.

Clinical Evaluations and Data Analysis:

Primary Outcome Measure: Itch scale: Visual Analog Scale for Itch (VAS Itch) Patients will score the severity of itch on the scale provided at study start, once weekly for 3 months, at the 3-month visit, and again at study end (6 months). Patients will rate their itch from 0 to 10.

Secondary Outcome Measures:

The Patient and Observer Scar Assessment Scale 3.0 (POSAS 3.0) will be filled out by the participant and a clinical observer to evaluate scar severity/quality at study start and again 3 months later. The POSAS provides subjective assessment of physical properties to be measured in this aim in addition to evaluation of sensory perceptions. The participant will rate whether the scar has been painful or itchy, evaluate various parameters of irregularity (e.g., color, stiffness, thickness), and provide an overall opinion of their scar. The health care provider will rate vascularity, pigmentation, thickness, relief, pliability, and surface area.

Scar volume: 3D photo taken with a LifeViz 3D II camera at study start and again 3 months later.

Elasticity, color, temperature, trans epidermal water loss, and scar thickness: measured with Dermalab combo (Cortex Technology, Denmark); each probe is held with constant pressure on the skin or scar surface for one minute; multiple measures are conducted to reduce variability at study start and again 3 months later.

Blood flow: measured via laser speckle with the PeriCam Perfusion Speckle Imaging (PSI) system at study start and again 3 months later. After a 6-minute acclimation to the temperature-controlled room (71ºF), patients lie supine during the one-minute scan. The machine head laser aperture should be positioned ~13 to 40 cm from the skin surface during the scan of each region. Color-coded speckle images are generated with measurements from the laser light reflected off the skin; the speckle image intensity fluctuates with blood cell movement. Four regions of both hypertrophic scar and non-burned skin are scanned (upper and lower extremities, dorsum of hand, and trunk) on each patient when possible. The percentage change in perfusion between adjacent non-burned skin and hypertrophic scar is determined; the data are log-transformed before analysis.

Overall activity: To be captured via Fitbit on a daily basis to gauge overall activity. These data will be correlated with the itch and pain scales as reduced activity is associated with pain and/or itch. This will occur throughout the entirety of the study.

Brisbane Burn Scar Impact Panel (BBSIP) is a patient-reported outcome measure developed in consultation with burn survivors that takes approximately 10 minutes to complete; the specificity of this comprehensive questionnaire allows detection of changes in quality of life related to burn hypertrophic scar. It will be administered at study start and again 3 months later.

Pain scale: Visual Analog Scale for Pain (VAS Pain) Patients will score the severity of pain on the scale provided at study start, at the 3 month visit, and again at study end (6 months). Patients will rate their pain from 0 to 10.

PROMIS-29 This questionnaire will be administered to determine whether the effects of treatment impact quality of life as reported by the patient at study start and again 3 months later.

Patient's Global Impression of Change: To assess participant satisfaction, this instrument consists of a single question that asks participants to rate the change in their condition (whether it has improved or deteriorated). This will be administered thrice – once before starting the study medication, at 3 months, and again at 6 months – to assess whether there was a change as a result of utilizing the therapies and then after ceasing them. The first administration will capture the effect of treatment, while the second administration will capture whether there was a change associated with cessation of treatment.

Skin Microbiome Analysis: To assess microbiome influence on itchy severity, skin swab will be collected at study start and at the 3-month visit. To investigate potential microbial differences associated with post-burn pruritus, skin swab samples will be collected from both the itchy burn scar and an area of unaffected contralateral skin from each participant. Each sample will be collected by gently rubbing the swab over a standardized skin area (e.g., 4–5 cm^2) for approximately 30 seconds. This procedure is non-invasive and well tolerated. After collecting, the swab tips will be aseptically placed into sterile 1.5 mL microcentrifuge tubes containing DNA/RNA preservation buffer (Zymo DNA/RNA Shield) and immediately stored at -80°C. Samples will be logged and stored by Dr Finnerty's Lab (Research Building 21, room 3408. Microbial DNA extraction and 16S rRNA gene sequencing will be performed by the Microbiome Sequencing Center at UTMB. Bioinformatic analysis will include comparisons of microbial diversity (alpha and beta diversity), taxonomic composition, and identification of differential taxa between itchy and non-itchy skin. Results will be interpreted in collaboration with microbiome data analysts and correlated with clinical itch severity scores.

6.0 Study Product Description

Formulation, Packaging, and Labeling

Identically packaged capsules will either contain 20mg famotidine or placebo. Similarly, lotion with or without 4% cromolyn sodium will be packaged identically.

Product Storage and Stability

There are no special requirements regarding product storage. Famotidine capsules have a shelf life of 6 months.

Dosage, Preparation and Administration of Study Intervention/Investigational Product
Capsules with placebo or famotidine (20mg) will be provided for oral administration twice daily.
A lotion, with or without 4% cromolyn sodium, will be provided for topical use twice daily.

Accountability Procedures for the Study Intervention/Investigational Product(s)
Capsules with famotidine or placebo, and lotion with and without 4% cromolyn sodium will be prepared by Greenpark Compounding pharmacy and provided to the UTMB investigational pharmacy.

Assessment of Participant Compliance with Study Intervention/Investigational Product
Compliance will be ascertained by pill audit, review of patient-maintained administration log.

Concomitant Medications/Treatments
Patients taking the following medications will be ineligible for participation: cefditoren, dasatinib, delavirdine, fosamprenavir, atazanavir, erlotinib, ketoconazole, itraconazole, ledipasvir/sofosbuvir, nilotinib, rilpivirine, cefuroxime, neratinib, pazopanib, risedronate, or tizanidine.

7.0 Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Rarely cromolyn sodium may induce an allergic reaction. As the typical administration routes are inhaled, nasal, or oral, additional side effects are specific to those routes of administration.

Adverse reactions to famotidine were largely similar to those experienced by the placebo group in controlled clinical trials. The following information was obtained from the PEPCID (famotidine) tablet package insert:

> "The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which PEPCID Tablets were compared to placebo, the incidence of adverse experiences in the group which received PEPCID Tablets, 40 mg at bedtime, was similar to that in the placebo group. The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).
> The following other adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to therapy with PEPCID has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:
> *Body as a Whole:* fever, asthenia, fatigue
> *Cardiovascular:* arrhythmia, AV block, palpitation
> *Gastrointestinal:* cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth
> *Hematologic:* rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia

Hypersensitivity: anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection
Musculoskeletal: musculoskeletal pain including muscle cramps, arthralgia
Nervous System/Psychiatric: grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence. Convulsions, in patients with impaired renal function, have been reported very rarely.
Respiratory: bronchospasm, interstitial pneumonia
Skin: toxic epidermal necrolysis/Stevens Johnson syndrome (very rare), alopecia, acne, pruritus, dry skin, flushing
Special Senses: tinnitus, taste disorder
Other: rare cases of impotence and rare cases of gynecomastia have been reported; however, in controlled clinical trials, the incidences were not greater than those seen with placebo. “

The potential risks from participation in the study are:

- Related to medication: Cromolyn sodium: Rarely cromolyn sodium may induce an allergic reaction. As the typical administration routes are inhaled, nasal, or oral, additional side effects are specific to those routes of administration. Famotidine: Side effects can include headache, constipation, diarrhea, dizziness, weakness, insomnia, muscle pain/cramps, dry mouth, nausea, vomiting.
- Related to the questionnaires: VAS, POSAS, BBSIP, Patient’s Global Impression of Change, PROMIS29: Minimal discomfort associated with answering questions associated with the questionnaire.
- Scar measurements: participant may experience discomfort related to laying still for scar measurements or from having their skin/scar touched.
- Related to loss of patient confidentiality. Chart review and patient history. The researchers will try to minimize these risks by coding study records with study numbers (as opposed to patient names or medical record numbers). The list decoding these assignments will have limited distribution. Electronic records will be kept on password-protected computers or servers. With respect to the Fitbit, because of the nature of the data and collection method, we cannot guarantee that data collected via this device will be confidential and it may be possible that others will know what has been reported.
- As with any research study, there may be additional risks that are unknown or unexpected.

The potential benefits to the patient that may result from participating in the study include decreased itch, improved function/mobility, and/or increased independence. The potential benefits to others would come in the future due to laying the groundwork to conduct studies to determine the efficacy of new anti-itch protocols.

Importance of the knowledge to be gained: The burn literature is replete with conclusions that H1 antihistamines do not reduce burn scar itch completely. We will now determine whether H2 antihistamines and cromolyn sodium can further suppress itch from the burn scar. If so, the results of this study will be used to inform a future clinical trial, which may

benefit other survivors of burn with itchy scars by adding new effective therapies to the burn care provider's armamentarium.

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate 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, which would include MD, PA, Nurse Practitioner, DO, or DDS), 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 patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

All AEs must be graded for severity and relationship to study product.

Severity of Event: All AEs will be assessed by the clinician using a protocol defined grading system. For events not included in the protocol defined grading system, than the following guidelines will be used to quantify intensity.

- Mild: events require minimal or no treatment and do not interfere with the patient'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 patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life threatening: any adverse drug experience that places the participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

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

Relationship to Study Products: The clinician's assessment of an AE's relationship to test article is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms: associated or not associated. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- Associated – The event is temporally related to the administration of the study product and no other etiology explains the event.

- Not Associated – The event is temporally independent of study product and/or the event appears to be explained by another etiology.

Serious Adverse Event (SAE): An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol defined surveillance
- Life-threatening event (defined as a participant at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. 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.

All SAEs will be:

- recorded on the appropriate SAE CRF
- followed through resolution by a study clinician
- reviewed and evaluated by a study clinician

Reporting Procedures
Any AE considered serious by the PI or Sub investigator or which meets the aforementioned criteria must be submitted on the SAE form to the IRB in accordance with IRB policies and procedures.

The study clinician will complete a sponsor provided Serious Adverse Event Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and sent by fax within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported via fax by the site within 72 hours of becoming aware of the event.

All SAEs will be followed until satisfactory resolution or until the PI or Sub investigator deems the event to be chronic or the patient to be stable.

8.0 Study Withdrawal/Discontinuation

Reasons for Withdrawal
A study participant will be discontinued from participation in the study if any of the following occur:

- Unacceptable toxicity or adverse event (AE)
- Unacceptable laboratory abnormalities
- Intercurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant in the opinion of the treating investigator
- Development of any exclusion criteria
- Participant withdrawals consent to continue in the research for any reason

Handling of Withdrawals

If a patient is withdrawn from the study due to a SAE, or if voluntary withdrawal occurs, the participant will be asked to continue with their clinical appointments, where continuing appropriate care under medical supervision will be provided until the symptoms of any AE resolve or the participant's condition becomes stable. Enrollment of an additional 4 subjects has been included to account for potential subject dropout.

Lost to Follow Up

The coordinator will communicate via phone and/or email to the participant to remind them of upcoming visits. A participant will be considered lost to follow up after they miss their scheduled visit, and the coordinator calls the participant on three separate occasions that are unsuccessful. The call attempts and the lost to follow up status will be documented in the participants research chart.

Termination of Study
Study will be terminated if the Data and Safety Monitoring makes the recommendation based on detection of unanticipated yet significant safety signal.

9.0 Statistical Considerations

This is a single-center, placebo-controlled, masked phase 3 trial of burned individuals with itchy burn scars in the outpatient setting. All participants will be adult survivors of burn, ≥18 to <80 years of age, and reporting itchy burn scar. Forty-four participants will be enrolled through the burn clinic at the University of Texas Medical Branch. Enrollees will participate in a 3 month-long program, with research assessments performed at the

start of the study and 3 months after study start. Participants will also be asked to answer a short survey 3 months following the completion of the study (6 months after study start). This study will test the efficacy of a multimodal approach to treating itch from burn scar. Participants will be randomized to one of two groups:

1. Placebo (recommended treatment with an H1 antihistamine and administration of placebo capsule and placebo lotion), or
2. PLUS (PLUS: recommended H1 antihistamine plus administration of famotidine and topical cromolyn sodium).

The University of Texas Medical Branch has a standing Data Safety Monitoring Board (DSMB) that was established to meet the needs of UTMB investigator-initiated studies requiring a DSMB. The board is tasked with providing services to ensure the ethical conduct of clinical trials and to ensure and protect the rights and safety of patients enrolled in a trial. The DSMB will meet annually to review the study, with additional meetings added if the need arises.

Our primary outcome of interest is difference in VAS itch from initial baseline measurement to VAS itch measurement at 12 weeks post treatment. Based on preliminary data from previous studies, [41-43] using a sample size of 20 individuals in the standard of care group and 20 individuals randomized to the dual treatment group, we will have 80% power to detect a significant difference in VAS itch differences using a two-sided student's t-test with an alpha of 0.05 assuming a mean difference in VAS itch scores to be 10.91 with an overall standard deviation of 12mm VAS itch. This power analysis was performed using PASS 2023. We will increase enrollment to 22 individuals per group in order to account for a 10% dropout rate.

Psychosocial outcomes may be modeled as discrete or continuous distributions, as appropriate, and may be transformed to better approximate normality. Separately at each time point, psychosocial outcomes will be modeled with relation to each physical measure (such as scar thickness, pliability, etc) and drug (placebo versus famotidine and cromolyn sodium) and an interaction between them, while adjusting for potentially prognostic covariates including gender, age, and total burned surface area, as well as date of measure (to control for evolving standard of care). The relationship between age, burn size, sex, and psychosocial outcomes will be examined. We expect larger burns result in more scar, increasing the probability of itch and female sex has been linked with greater itch following burn, as has older age.

Generally, multiple analysis of variance models will be used, blocking on participant to control for repeated measures, however where model residuals suggest the presence of non-linear relations between the outcome and physical measure we will use generalized additive models to accommodate the nonlinear relation with penalized splines. Additional models will be considered where supported by sufficient data, to explore in a more nuanced manner how the treatment effect varies with sex, age, and burn size on the outcome.

10.0 Ethics and the Protection of Human Participants

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the

Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

The investigator must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate independent ethics committee (IEC) or IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States and in other countries, only institutions holding a current US Federalwide Assurance issued by OHRP may participate.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. 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.

Privacy/Confidentiality Issues

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

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 Principal investigator.

Individuals authorized to view study records will be identified to the study participant on the informed consent but may include a study monitor or other authorized representatives of the sponsor or funding agency or federal or local agencies that regulate research including representatives from the Food and Drug Administration, Office of Human Research Protections, or the Institutional Review Board. Study records may also be made available for internal compliance reviews and quality assurance representatives.
These individuals 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.

In accordance with the Food and Drug Administration Amendment Act of 2007 (FDAAA) and The International Committee of Medical Journal Editors (ICMJE) member journals trials-registration policy as a condition for publication, this study will be registered in the public trials registry ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Results will be published to clinicalTrial.gov when available but will not identify individual participants.

11.0 Record Retention

Records shall be retained according to ICH or applicable local regulatory requirements, whichever is longer. Investigator shall determine the disposition of the data after such retention period in accordance with its internal policies and any other of its legal or regulatory requirements.

If a research study accesses protected health information (PHI) and is covered under the Health Insurance Portability Accountability Act (HIPAA), consent forms that include the HIPAA Authorization are to be retained for a minimum of 6 years from the date of the authorization.

Research records will be maintained in accordance with the current version of the Texas Health Records Table 17-III Record Retention Schedule, Human Subject Research Records and Documents.

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