An Open-label Pilot Study to Evaluate the Effectiveness and Tolerability of a Topical Composition Therapy for the Treatment of Cutaneous Mastocytosis

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Study Site Location:	Mayo Clinic Department of Allergy 200 SW 1st Street Rochester, MN
IRB Number:	20-011876
IND Number:	146547
Study Product:	"Skin Guard" topical cream formulation containing: Diphenhydramine 1% Trolamine Salicylate 10% Cromolyn sodium 5% Vanicream

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Study Summary

Title	AN OPEN-LABEL PILOT STUDY TO EVALUATE THE EFFECTIVENESS AND TOLERABILITY OF A TOPICAL COMPOSITION THERAPY FOR THE TREATMENT OF CUTANEOUS MASTOCYTOSIS
Running Title	Topical Composition for Cutaneous Mastocytosis
Protocol Number	Pending
Phase	Phase II Feasibility/Proof of Concept
Methodology	Open Label
Subject participation Duration	Two weeks
Study Duration	One year
Single or Multi-Site	Single Center
Objectives	To determine the effectiveness and tolerability of a novel topical preparation for the treatment of cutaneous lesions of mastocytosis.
Number of Subjects	10
Diagnosis and Main Inclusion Criteria	Cutaneous mastocytosis
Study Product, Dose, Route, Regimen	Topical composition 'Skin Guard' applied twice daily for four weeks.
Duration of Administration	2weeks

1 Introduction

This human clinical research study will be carried out in accordance with the protocol, applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Condition to be studied

Mastocytosis is a rare disorder of clonal mast cell proliferation. There are several subclasses of systemic mastocytosis (SM) ranging from indolent disease to aggressive disease, mast cell leukemia and mast cell sarcoma. The major criterion for defining systemic disease is the presence of mast cell (MC) infiltration of organs (commonly assessed by tissue or bone marrow biopsy). Patients with SM may or may not have cutaneous involvement. Whereas in cutaneous mastocytosis (CM), MC infiltration is limited to the skin.

Why the investigational product may be beneficial

Topical treatment of symptoms resulting from cutaneous involvement by mastocytosis (pruritus, flushing, urticaria, angioedema) is mainly limited to topical lubricants, topical corticosteroids, and topical antihistamines, medications that have individually been available for decades. In our own experience, topical cromolyn sodium 0.25% (children), and 1% or 5% (adults) can also be effective for relief of dermal symptoms.

Excessive application of topical steroids can cause skin atrophy or delayed healing, while excessive absorption of topical antihistamines could lead to systemic side effects such as somnolence, dyskinetic symptoms, impairment of performance skills, anticholinergic symptoms and others.

The product to be used will not contain corticosteroids and will use a lower concentration of diphenhydramine (1% vs 2%) than is currently available in over the counter preparations. By combining 3 ingredients, diphenhydramine, cromolyn sodium and trolamine we will leverage the different effects of various classes of medications to block mast cell mediator release (cromolyn sodium), to block mediator (histamine) receptors (diphenhydramine) and to inhibit production of prostaglandin D2 by topical cyclooxygenase blockade (trolamine salicylate).

Pathophysiology relevant to potential study treatment action

Symptoms from mastocytosis result from accumulation of these cells as well as local and remote effects of MC mediators. Mast cells are dynamos for the production of mediators that in the skin can stimulate symptoms by their effects on blood vessel constriction, vasopermeability, and excitation of nerve endings causing itching, hiving, swelling and flushing. The synergistic effect of targeting 3 of the most prevalent (and measurable) mediators should have a beneficial effect on dermatologic symptoms and will allow a lower

concentration (1% vs 2%) of diphenhydramine to be used than is commonly employed in OTC topical preparations of this medication.
Description of the population to be studied

Involvement of the skin in mastocytosis is equally common in men and women. Patients age 18 and above with CM or skin involvement in SM confirmed by skin biopsy who have bothersome, symptoms not controlled with topical and systemic medications will be eligible to participate in this study. Ten patients will be enrolled. Women who are pregnant or nursing will be excluded.

1.2 Investigational Agents

The proposed study refers to a topical composition of the following agents, each of which is currently approved for and is used in clinical practice:

DIPHENHYDRAMINE

Drug Class:H1 antihistamine

Mechanism of Action Diphenhydramine acts as an antihistamine by competing with histamine for receptor sites on effector cells such as mast cells and basophils.

Pharmacology Diphenhydramine is a first generation antihistamine of the ethanolamine class. It has antimuscarinic, antiemetic and sedative effects and competitively antagonizes the effect of histamine on histamine receptors in the GI tract, uterus, large blood vessels, and bronchial muscle. It has multiple other uses such as treating drug-induced extrapyramidal effects, vertigo and Meniere's disease. Diphenhydramine is metabolized in the liver and the total body clearance of orally administered diphenhydramine is 11.7 to 49.2 mL/min/kg.

TROLAMINE SALICYLATE

Drug Class: Non-steroidal anti-inflammatory

Mechanism of Action: The active moiety in trolamine salicylate is salicylic acid which, by inhibition of prostaglandin synthesis inhibits pain, inflammation and hyperemia. The downstream effect of inhibition COX-1 includes blocking synthesis of prostaglandin (PG) D2, a product of mast cells.

Pharmacology: Available as an over-the-counter preparation, 10% topical trolamine salicylate is commonly used to treat musculoskeletal pain and osteoarthritis.

CROMOLYN SODIUM (disodium cromoglycate)

Drug Class: Anti inflammatory agent and mast cell stabilizer.

Mechanism of Action: Cromolyn sodium blocks the release of histamine and SRS-A (slow-reacting substance of anaphylaxis) from sensitized mast cells.

Pharmacology: Cromolyn sodium is available in multiple dosage forms including an oral form used for treating gastrointestinal disorders in hypereosinophilic disorders and in mastocytosis; ophthalmic drops for treating allergic conjunctivitis; a nasal spray for treating allergic rhinitis; an inhalant solution for treating asthma, and is prepared in a compounded topical cream for treatment of cutaneous mastocytosis. Oral cromolyn sodium is poorly absorbed and the bioavailability of inhaled (8%), ophthalmic (0.03%), and oral (not more than 1%) is low. In one study of the absorption of oral [^{14}C] disodium cromoglycate only 0.4% of an oral dose (20 mg) appeared in the 24 hr urine sample and 83% was recovered from the feces. While intravenous administration resulted in approximately equal amounts (30-50%) being excreted via the urine and feces (Walker SR, Evans ME, Richards AJ, Paterson JW. The fate of [^{14}C] disodium cromoglycate in man. J. Pharm. Pharmac.1972; 24: 525-531)

VANICREAM (OTC)

Drug Class: Moisturizer; Vehicle for topical preparations

Mechanism of Action: Vanicream is used as a topical lubricant that does not clog pores and is not absorbed. It is used by itself as a moisturizer and for compounding of topically applied skin care products.

Pharmacology: Vanicream is formulated as an OTC preparation comprised of: purified water, white petrolatum, sorbitol solution, cetearyl alcohol, propylene glycol, ceteareth-20, simethicone, glyceryl monostearate, polyethylene glycol monostearate, sorbic acid, BHT. It is free of lanolin, fragrances, parabens and formaldehyde. Vanicream is compatible with numerous topical agents used for skin care.

2 Study Objectives

The primary objective of this study is to assess the effectiveness of twice daily application of trolamine salicylate 10%, sodium cromolyn 5%, and diphenhydramine 1% on symptoms resulting from cutaneous mastocytosis.

3 Study Design

3.1 General design

This is a phase II nonrandomized, open-label pilot study of the effectiveness and tolerability of a novel composition comprised of daily application of trolamine salicylate 10%, sodium cromolyn 5%, and diphenhydramine 1% in vanicream on skin producing cutaneous symptoms of mastocytosis. Subjects will be screened by the Department of Allergic Diseases at the Mayo Clinic in Rochester MN and interested qualified subjects will be consented and offered participation. The study is designed to establish

feasibility/proof of concept and will not include randomization or crossover components. Please see Section 6: Study procedures for a detailed description.

3.2 Primary Study Endpoints

Scorma Index[see below]
The proportion of participants who achieved complete resolution or near-complete clearing of cutaneous symptoms of treated, involved skin after 2 weeks' treatment will be evaluated using the SCORing MAstocytosis (SCORMA) index. SCORMA has been utilized to evaluate the severity of cutaneous mastocytosis and to correlate with serum tryptase levels. Repeated SCORMA determinations can "provide a rapid impression of changes in the clinical status" in mastocytosis (HeideR, van Doorn K, Mulder PG et al. Serum tryptase and SCORMA (SCORing MAstocytosis) index as disease severity parameters in childhood and adult cutaneous mastocytosis. Clinical and Experimental Dermatology 2008; 34: 462-468.)
The SCORMA index is calculated by the formula A/5 +5B +2C/5 where
A=Extent of skin involvement,
B= Intensity (pigmentation/erythema + vesiculation + elevation + positive Darier's sign each rated 0[absent], 1[mild] 2[moderate] or 3[severe]).
C= subjective symptoms utilizing visual analog scale 1-10 of the following: provoking factor(s), flushing, diarrhea, pruritus, localized bone pain.

Since it will be impractical for patients to apply Skin Guard to the entire body surface area, and not all areas of the skin will be involved to the same extent, we will limit application to between 9% and 18% of the skin (see SCORMA figure). In this regard we will attempt, when possible, to utilize equally involved sides of the torso or extremities to facilitate evaluation of effectiveness. We will generate not only a "Global" SCORMA value, but in addition a SCORMA value for the treated, involved skin. The latter should give a more accurate estimation of the effectiveness on treated areas.

Quality of Life –SkinDex-16[see below]. Skindex-16, a validated measurement of the effects of skin diseases on patients' quality of life will be utilized to follow this parameter. SkinDex has been used and adapted for dermatologic research internationally (Chren M-M, The SkinDex instruments to measure the effects of skin disease on quality of life. Dermatology Clinics 2012; 30: 231-236).

3.3 Secondary Study Endpoints

These will include mast cell mediator levels; serum tryptase, urinary leukotriene (LT) E4, n-methyl histamine (N-MH), and 2,3 dinor 11β prostaglandin(PG) F2α levels [Mayo Medical Labs].

3.4 Primary Safety Endpoints

Minimal systemic absorption is expected with each of the active components. Safety endpoints to be measured at the initial and final visits and include Investigator and Participant observation of local skin tolerability including ratings of itching, swelling

stinging/ burning, and dryness on separate scales as none (0), mild (1), moderate (2), or severe (3).

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion criteria

Informed subject consent will be obtained from those patients with the following inclusion criteria:

- Biopsy proven cutaneous mastocytosis with or without evidence of systemic disease
- Male and female patients 18 to 80 years of age
- No UVB treatment of the skin for 6 months prior to study entry
- No use of topical or systemic corticosteroids for 1 month prior to study entry
- Good general health as confirmed by medical history
- Female patients of child-bearing potential with negative urine pregnancy test who agree to use effective methods of birth control or remain abstinent during treatment. Participants must use birth control for the entire study and for at least 1 week after the last application of the study formulation. Acceptable methods of birth control include ongoing hormonal contraception methods, (such as birth control pills, patches, injections, vaginal ring, or implants), barrier methods (such as a condom (for men) or diaphragm used with a spermicide), intrauterine devices, tubal ligation, or abstinence.
- Patients who are willing and capable of cooperating to the extent and degree required by the protocol; and
- Patients who read and sign an approved informed consent for this study

4.2 Exclusion criteria

Patients are to be excluded based on the following criteria:

- Vulnerable study population
- Exposure to ultraviolet B (UVB) radiation to any region of the skin surface for 6 months
- Regular use of skin lightening agents within 1 month of study entry, including
  - Topical corticosteroids
  - Topical bleaching products
  - Topical retinoids
- Use of systemic preparations within 1 month of study entry, including:
  - Systemic corticosteroids
  - Systemic cyclosporine, interferon
  - Systemic acitretin, etretinate, isoretinoin
  - Systemic methotrexate,
  - Systemic photoallergic, phototoxic and/or photosensitizing drugs
- UV light therapy and sunbathing

●Inability to communicate or cooperate with the Principal Investigator and/or Investigators due to language problems, poor mental development or impaired cerebral function
●Pregnant or nursing women
●Women planning a pregnancy within the study period

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited from the Division of Allergic Diseases at the Mayo Clinic in Minnesota outpatient clinical practice. Patients will be provided with a Research Participant Consent and Privacy Authorization Form describing the study formulation, protocol, inclusion and exclusion criteria, as well as risks and benefits of participation.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Patients are free to withdraw at any time and for whatever reason. No data will be collected for withdrawn subjects and withdrawn subjects will not be replaced. There will be no follow-up for withdrawn subjects. Pre-specified reasons for discontinuing include, but are not limited to, the following:

● Patient request: Patient decided that he/she did not want to continue (for any reason).
●Adverse Event: Patient experienced a related or unrelated event that would interfere with the study objectives/evaluation
●Lost to Follow-up: Patient did not come in for a visit and could not be reached by phone
●Treatment Failure: If in the Principal Investigator's judgment, the patient's condition required another form of treatment
●Noncompliance: Patient is not complying with the protocol requirements (i.e. visit schedule, dosing, regimen, etc.); a patient is to be withdrawn if he/she misses two consecutive visits
●Other: Any other reason

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a Participant withdraws from the study, no additional attempts will be made to contact the Participant.

5 Study Drug

5.1 Description

The "skin guard" study formulation is a combination of components of FDA approved drugs trolamine salicylate 10%, sodium cromolyn 5%, and diphenhydramine 1% as well as the skin moisturizer Vanicream (OTC). The components will be compounded into a cream formulation and is intended for topical application to the skin. The drug product will be packaged in a polypropylene ointment jar with screw cap lid.

5.2 Study Procedures

Preparation and Administration of Study Drug

Each participant will receive both verbal and written instructions as to proper dosing and application and storage. The Mayo Clinic Research Pharmacy in Rochester, MN will prepare, store and distribute the study formulation. Participants will receive 2-one-half pound ointment jars of the study formulation. The jars will be returnedat the final visit.. The returned used jars will be weighed by the Principal Investigator or a study team member to determine the amount used/compliance. Should additional cream be required during the 2 weeks of the study, the patient can contact the principal investigator or the clinical study coordinator. Upon notification from the patient, an extra ½ pound jar will be sent to the patient by overnight express mail.

Instructions will be provided as follows: Twice daily, apply a thin film of the study formulation to symptomatic areas of the skin including about one centimeter of normal appearing skin surrounding each area of involvement. Rub lightly and uniformly into the skin. An investigator will demonstrate correct application by using a bland emollient moisturizer.

Subject Compliance Monitoring

Adherence to the treatment regimen is of great importance. Poor compliance may result from lack of patient understanding, discomfort caused by the product and unrealistic expectations. Assessment of participant compliance will be determined by weighing ointment jars at the time of the final visit. Participants are not expected to use a specific amount of the study formulation . Rather, use will be individualized depending on the amount of symptomatically involved skin. Those who are non-compliant with the study protocol despite additional counseling and the opportunity to correct will be withdrawn.

5.3 Prior and Concomitant Therapy

With the exception of ordinary over-the-counter moisturizers, and sun protection, no concomitant topical medicines/therapies are permitted for 1 month prior to and during the study period.

5.4 Packaging

The study formulation will be packaged in a ½ pound ointment jar with screw lid. The jars of drug product will be labeled with each subject's name, active contents, expiration, lot number and the following statement: "*EXTERNAL Use Only* *For investigational Use Only*".

5.5 Masking/Blinding of Study

This is an open-label pilot investigation. Masking/blinding procedures are not applicable. Qualitative and quantitative evaluations of response to treatment will be recorded. Updated photographs will be included in participants' records time 0, and week 4.

5.6 Receiving, Storage, Dispensing and Return

5.6.1Receipt of Drug Supplies: The study formulation will be compounded by the Mayo Clinic Research Pharmacy in Minnesota for each subject.

5.6.2 Storage: The study formulation will be stored at room temperature 68º to 77º F (20º-25ºC), with excursions permitted between 59º to 86ºF (15º-30ºC), by the Mayo Clinic Research Pharmacy in Minnesota. There are no special handling requirements.

5.6.3 Dispensing of Study Drug: Finalreconciliation by weight measurement and/or number of returned empty jars will be performed by the Principal Investigator or study team member to document study formulation dispensed and returned. This reconciliation will be logged on the Case Report Form, and signed and dated by the Principal Investigator and/or investigators.

5.6.4 Return or Destruction of Study Drug: At the completion of the study, there will be a final reconciliation of the study formulation dispensed, returned and remaining. This reconciliation will be logged on the Case Report Form, signed and dated. Any discrepancies noted will be documented and investigated. Drug destroyed on site will be documented. Participants will be required to return any unused study drug at the end of the study period.

6.1 Visit 1 (Week 0/Baseline)

a) Assess degree of cutaneous involvement by SCORMA Index; Indicate area(s) of the skin to be treated; generate "Global" and "Local" SCORMA values; physical exam/vital signs
b) Obtain β-HCG. Obtain baseline levels of tryptase, urinary N-MH, LTE4, and 2,3 dinor 11β PGF2α if (not obtained during prior 6 months).
c) Review medical history and current medications
d) Informed consent
e) Patient to complete Quality of life questionnaire-SkinDex-16.
f) Baseline photographs
g) Review treatment protocol
h) Dispense study formulation

6.5 Visit 2-Final visit (Week 2 +/- 1 day)

a) Reassess cutaneous mastocytosis severity by (Global & Local) SCORMA Indexes; monitor vital signs
b) Investigator Assessment of Global Improvement
c) Quality of life assessment:SkinDex-16
d) Review changes to medical history and current medications
e) Review contraception (female patients of childbearing potential)
f) Review adverse events
g) Review compliance

h) Repeat photographs
i) Obtain levels of serum tryptase, urinary N-MH, LTE4, and 2,3 dinor 11β PGF2α
j) Reconcile study formulation

6.6 Protocol Schedule of Events

Study Activity	Week 0 Screening & Baseline	Week 2
Visit Number	1	2
Allowable visit window in days		+/- 1
Review Eligibility	X	
Informed Consent	X	
Medical History	X	X
Dispense/Reconcile Medications	X	X
Review Changes to Medical History and Medications		X
Quality of Life Scale:SkinDex-16	X	X
SCORMA Index	X	X
Physical Exam	X	
Serum Tryptase, & urinary Mast cell mediators	X	X
Investigator Assessment of clinical response: initial and subsequent; vital signs	X	X
Photography	X	X
Adverse Event (Physician)		X
Adverse Event (Participant)		X
Review Dosing Compliance		X
Review Contraception	X	X
β-HCG[a]	X	
a: Urine pregnancy test (women of childbearing potential)		

7 Statistical Plan

7.1 Sample Size determination

Due to the pilot nature of the study, no formal statistical power/sample size calculations are necessary. The sample size of 10 patients will be sufficient for this pilot study to obtain a preliminary estimate of treatment efficacy and to generate data that will be useful in the design of a larger study.

7.2 Statistical Methods

Continuous variables will be summarized using the sample mean, median, standard deviation, interquartile range, and range. Categorical variables will be summarized using number and percentage of patients.

7.2.1 Definition of response

Complete response:

Clinically significant SCORMA improvement in all 3 parameters of treated, involved skin: % skin involvement; activity or symptoms &/or
Improvement in all 3 SkinDex-16 domains (Emotions, symptoms, functioning) &/or
Resolution of 75% of cutaneous lesions

Near Complete response:

Clinically significant SCORMA improvement in two of 3 parameters of treated, involved skin: % skin involvement; activity or symptoms and/or
Improvement in 2 SkinDex-16 domains (Emotions, symptoms, functioning) &/or
Resolution of >50% of cutaneous lesions

Partial Response:

Clinically significant SCORMA improvement in one 3 parameters of treated, involved skin: % skin involvement; activity or symptoms and/or
Improvement in 1 SkinDex-16 domain (Emotions, symptoms, or functioning) &/or
Resolution of >25% of cutaneous lesions

No response:

No significant SCORMA improvement in any of 3 parameters of treated, involved skin: % skin involvement; activity or symptoms and/or
Improvement in no SkinDex-16 domain (Emotions, symptoms, functioning) &/or
Resolution of no cutaneous lesions.

*Additionally, for primary safety endpoints which will be scored as none, mild, moderate, or severe, the proportion of patients in each category at each follow-up time point will be estimated for each of the different safety endpoints. P-values of 0.05 or lower will be considered as statistically significant.

Handling of missing data

This is a prospective study and therefore we do not anticipate any missing data. In the event of any unexpected missing data, no attempt to impute this missing data will be made; missing data will simply be treated as missing in the statistical analysis.

Multiplicity

Since this is an exploratory pilot study, no adjustment for multiple testing is needed. P-value of 0.05 or lower will be considered as statistically significant.

Primary Hypothesis:

The study seeks to demonstrate the effectiveness and tolerability of a novel topical composition consisting of 3 components (diphenhydramine, aspirin and cromolyn sodium) in a neutral skin moisturizing cream (Vanicream) for the treatment of cutaneous lesions of mastocytosis. This will be determined by the proportion of participants who achieve complete or near-complete response utilizing the SCORMA Index, and SkinDex-16 QOL.

We will use the SCORMA index and SkinDex-16 as both continuous variables and categorical variables. Change in SCORMA and of SkinDex-16 from baseline to the 2week follow-up visit will be estimated using sample mean, median, standard deviation, interquartile range, and range. SCORMA and SkinDex-16 will be compared from baseline to the follow-up time point using a paired Wilcoxon signed rank test.

Interim Analysis

There will not be any interim analysis given the low risk profile of the study formulation.

7.3 Subject Populations(s) for Analysis

Each participant who received the study drug will be included in the primary analysis regardless of study withdrawal for any reason. In the event of any study withdrawals, in secondary analysis we will examine the sensitivity of our results to the exclusion of patients who withdrew.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

●Serious: Serious problems or events that result in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization- inpatient, new, or prolonged; (4) disability/incapacity-persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the Principal Investigator and/or Investigators may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

●Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Research Participant Consent and Privacy Authorization Form, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**

●Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of the study formulation in a research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events are defined as events that:

- result in death
- are immediately life threatening
- result in a new or prolong and existing hospitalization
- result in disability/incapacity; or
- are persistent or significant birth defect/anomaly

And/or per protocol may be problems/events that in the opinion of the Principal Investigator and/or Investigators may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromise the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as non-serious events.

Adverse Event Reporting Period
For this study, the study treatment follow-up period is defined as the last scheduled visit.

Preexisting condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events are to be followed by the Principal Investigator and/or Investigators until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the Principal Investigator and/or Investigators should instruct each subject to report and any subsequent event(s) that the Participant, or the Participant's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality that can reasonably be related to the administration of the study formulation should be documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery
Hospitalization, prolonged hospitalization, or surgery is to be reported as an adverse event if it can reasonably be related to the administration of the study formulation.

8.2 Recording of Adverse Events

At each contact with the subject, the Principal Investigator and/or Investigators 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 appropriate adverse event section of the Case Report Form. All clearly related signs and symptoms should be recorded.

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 ultimately determined that the study treatment or participation is not the probable 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 at least possibly related to the study treatment or study participation will be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When and adverse event has been identified, the Principal Investigator and/or Investigators will take appropriate action necessary to protect the study participant and then document the event in the adverse event section of the Case Report Form. The Principal Investigator and/or Investigators will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Investigator reporting: notifying the Mayo Clinic IRB

The Principal Investigator and/or Investigators will report, as soon as possible, but no later than 5 working days after first learning of the problem/event, to the Mayo Clinic IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo Clinic IRB Policy and Procedures.
Documentation of adverse events will include the following information collected in the adverse event section of the case report form (and entered into the research database):
●Subject's name
●Medical record number
●Disease
●The date the adverse event occurred
●Description of the adverse event
●Relationship of the adverse event to the research
●If the adverse event was expected
●The severity of the adverse event (defined by a severity scale)
●If any intervention was necessary
●Resolution (was the incident resolved spontaneously, or after discontinuing treatment)
●Date of resolution

The Principal Investigator and/or Investigators will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The Principal Investigator and/or Investigators will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.3.2 Investigator reporting: Notifying the FDA

This protocol is being conducted under an FDA investigational new drug application.
The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.
Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.
Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.
Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.
The sponsor-investigator must also notify the FDA (and sponsors must notify all participating investigators) in an 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 under § 312.32(c)(1)(i)-(iv).
Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4 Unmasking/Unblinding Procedures

This is an open-label pilot investigation. Unmasking/unblinding procedures are not applicable.

8.5 Stopping Rules

This investigation is of low risk to study subjects. Stopping or interruption of the study may be necessary if a significant number of participants develop an unexpectedly severe dermatitis that does not resolve with decreased frequency of application.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator and Investigators to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPPA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the Principal Investigator and Investigators, by regulation, retain the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, micorfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

All source documents including clinical findings, observations or other activities will be stored in a REDCap database that will be designated by the Statistician. Access to the REDCap database will be limited to the Principal Investigator, Investigators, and Statistician.

9.3 Case Report Forms

All data requested on the Case Report Form (CRF) will be recorded for each participant. A standardized CRF will be generated by REDCap. All missing data will be explained. If a space on the CRF is left blank because the question was not asked, "N/D" will be recorded. If the item is not applicable to the individual case, "N/A" will be recorded. If any entry error has been made, a single straight line through the incorrect entry will be drawn and the correct data will be written above it. All such changes will be initialed and dated. Errors will not be erased or whited-

out. For clarification of illegible or uncertain entries, a clarification will be printed above the item, then initialed and dated. If the reason for the correction is not clear or needs additional explanation, details to justify the correction will be neatly included.

Data Management, Processing, Security and Confidentiality

Study data to be collected and managed using REDCap electronic data capture tools hosted at the Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Data Quality Assurance

Once the study is completed the Principal Investigator will randomly select 5 participants and compare the data documented for each on the CRF with what is entered into the REDCap database. If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 10 patients to ensure accuracy.

Data Clarification Process

For any data query the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus.

9.4 Records Retention

The Principal Investigator and Investigators will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. Participant names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

The Principal Investigator will retain the specified records and reports for a minimum of five years after final study closeout, and original data will be retained, if possible.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The Principal Investigator will allocate adequate time for such monitoring activities. The Principal Investigator will also ensure that the monitor or other compliance of quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.). The Mayo Clinic Office of Research Regulatory Support will assist with study monitoring by review of informed consent documents, subject records and

study Regulatory Documents. Some monitoring may be done remotely, using the electronic medical records. Written monitoring reports will be issued to the PI.

10.2 Auditing and Inspecting

The Principal Investigator and Investigators will permit study-related monitoring, audits, and inspections by the IRB, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Principal Investigator and Investigators will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Mayo Clinic institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the Principal Investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form is to be signed by the participant and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study is to be financed by the Mayo Clinic.

13 Publication Plan

The Principal Investigator and Investigators hold primary responsibility for publication of the results of this study.

14 References

The following references serve to define criteria for systemic and cutaneous mastocytosis

Akin C, Valent P. Diagnostic criteria and classification of mastocytosis in 2014. Immunol Allergy Clin North Am. 2014;34(2):207-18.

Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. European journal of clinical investigation. 2007;37(6):435-53.

Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol. 2012;157(3):215-25.

The following references serve to document the use of cromolyn sodium in the treatment of cutaneous mastocytosis

Horan RF,Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. J. Allergy Clin Immunol 1990; 85: 852-858.

Alexander RR. Disodium cromoglycate in the treatment of systemic mastocytosis involving only bone. Acta haemat 1985; 74: 108-110.

The following references serve to document the use of topical and systemic antihistamines in the treatment of mastocytosis.

Friedman BS, Santiago ML, Berkebile C, Metcalfe DD. Comparison of azelastine and chlorpheniramine in the treatment of mastocytosis. J. Allergy Clin Immunol 1993; 92; 520-526.

Hadzijusufovic E, Peter B, Gleixner KV, Such K, Pickl WF, Thaiwong T et al. H1-receptor antagonists terfenadine and loratadine inhibit spontaneous growth of neoplastic mast cells. Experimental hematology 2010; 38: 896-907.

The following reference serves to document the use of the SCORMA index to evaluate disease severity of cutaneous mastocytosis

HeideR, van Doorn K, Mulder PG et al. Serum tryptase and SCORMA (SCORing MAstocytosis) index as disease severity parameters in childhood and adult cutaneous mastocytosis. Clinical and Experimental Dermatology 2008; 34: 462-468.

The following references serve to document the use of SKINDEX to measure QOL in patients with skin diseases

Chren M-M, The Skindex instruments to measure the effects of skin disease on quality of life. Dermatology Clinics 2012; 30: 231-236.

Chren M-M, Lasek RJ, Sahay AP, Sands LP. Measurement properties of skindex-16: a brief quality-of-life measure for patients with skin diseases. Journal of Cutaneous Medicine and Surgery 2001; 5: 205-110.

The following references serve to document the use of aspirin and/or nonsteroidal medications in the treatment of symptoms of mast cell activation and mastocytosis

Wong JT, Nagy CS, Krinzman SJ, MacLean JA, Bloch KJ. Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema . J Allergy Clin Immunology 2000; 105: 997-1001.

Butterfield JH. Survey of aspirin administration in systemic mastocytosis. Prostaglandins Other Lipid Mediat. 2009;88(3-4):122-4.

Butterfield JH, Weiler CR. Prevention of mast cell activation disorder-associated clinical sequelae of excessive prostaglandin D(2) production. Int Arch Allergy Immunol. 2008;147(4):338-43.

Butterfield JH, Kao PC, Klee GC, Yocum MW. Aspirin idiosyncrasy in systemic mast cell disease: a new look at mediator release during aspirin desensitization. Mayo Clin Proc. 1995;70(5):481-7.

The following reference serves to document the combined use of antihistamines and cyclooxygenase inhibition in the treatment of systemic mastocytosis

Crawhall JC, Wilkinson RD. Systemic mastocytosis: management of an unusual case with histamine (H1 and H2) antagonists and cyclooxygenase inhibition. Clinical and Investigative Medicine 1987; 10: 1-4.

15. Attachments:

a) Advertisement
b) Patient Handout
c) QOL questionnaire

ADVERTISEMENT

An Open-label Pilot Study Evaluating the Effectiveness and Tolerability of a Topical Therapy for the treatment of Cutaneous Mastocytosis

A Mayo Clinic Research Study

Mayo Clinic is seeking ten individuals with skin involvement by mastocytosis to participate in a research study.

The purpose of this study is to gather information on the effectiveness and tolerability of a novel composition of existing U.S. Food and Drug Administration (FDA) approved topical medications for the treatment of cutaneous mastocytosis with or without systemic involvement.

You may be eligible to participate if you meet the following criteria:
●18 years of age and older
●Bothersome symptoms from skin involved by mastocytosis
●No prior use of topical skin –lightening agents for 1 month prior to study entry
●No current use of Interferon Alpha; Cladribine; Imatinib Mesylate; Midostaurin; Avapritinib, Prednisone or other chemotherapy agents.
●No current use of chemotherapeutic agents
●Good general health as confirmed by medical history
●Female patients of childbearing potential with a negative urine pregnancy test who agree to use effective methods of birth control or remain abstinent during treatment
●Patients who are willing and capable of cooperating to the extent and degree required by the protocol
●Patients who read and sign an approved informed consent for this study

The study includes 2 visits over 2weeks. There will be no cost to participate. You will not be compensated for your time.

Who can I contact for more information?

Principal Investigator: Joseph H. Butterfield, M.D.	**Phone:** 507-2843783 **Email:** Butterfield.joseph@mayo.edu **Address:** W15B Mayo Clinic 200 SW 1st Street Rochester, MN 55901

Primary Safety Endpoints Table

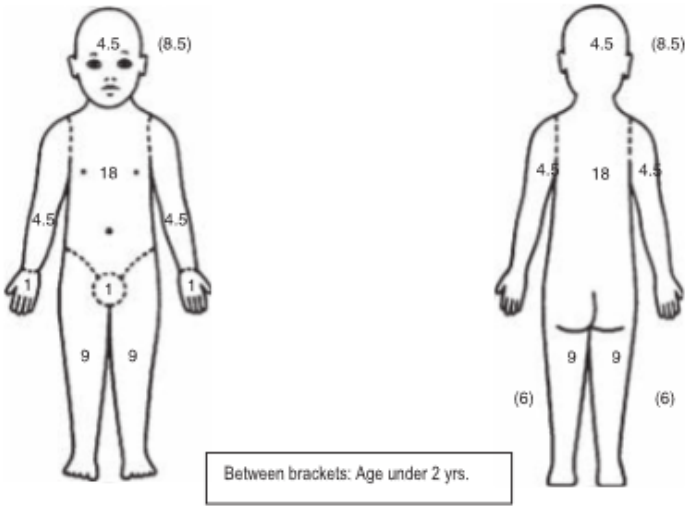
Patient Name:

Symptom (Patient/Physician)	Week→	
	0	2
itching		
swelling		
stinging/burning		
dryness		

none (0), mild (1), moderate (2), or severe (3)

SCORMA INDEX

Institution	:	Name of patient	:
Physician	:	Date of birth	:
Date of visit	:	Patient number	:



Between brackets: Age under 2 yrs.

A: Extent please indicate the area involved [ ]

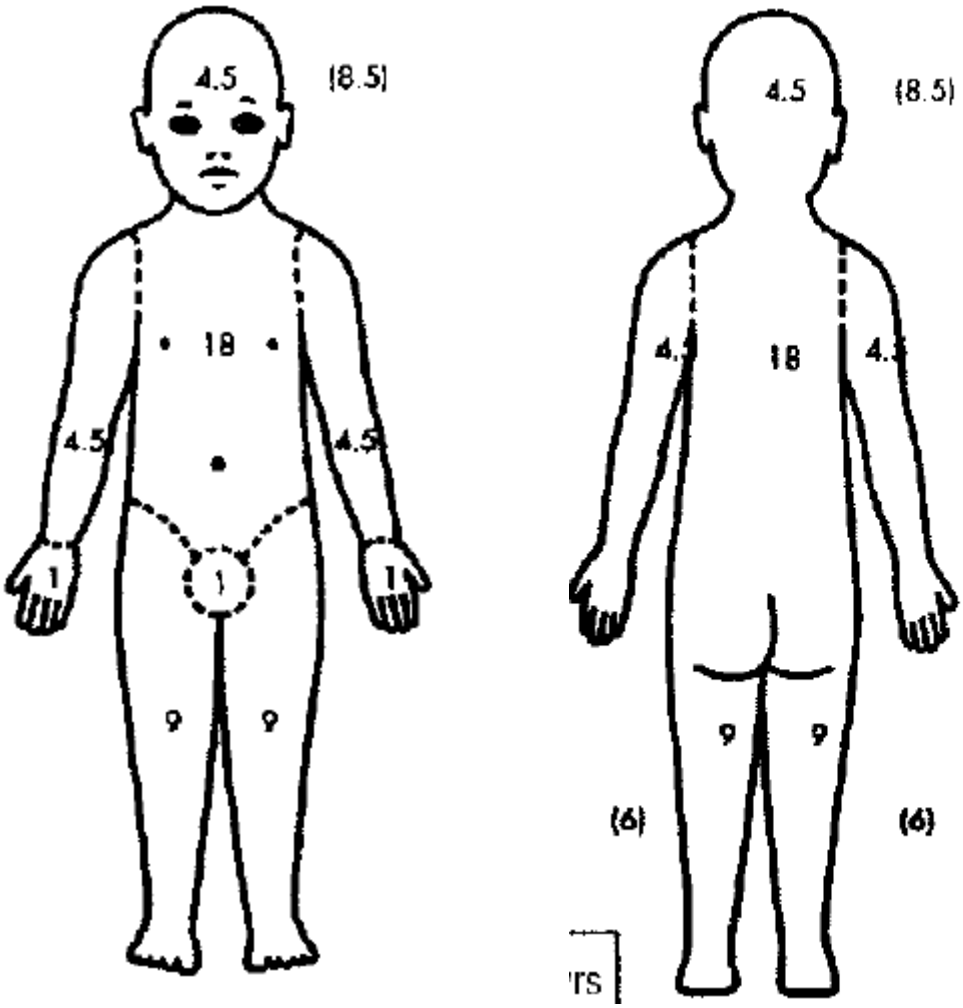
B: Intensity average representative area [ ]

Criteria	Intensity	Intensity items
1. Pigmentation / erythema	[ ]	0 = absent
2. Vesiculation	[ ]	1 = mild
3. Elevation	[ ]	2 = moderate
4. Positive Darier's sign	[ ]	3 = severe

C: Subjective Symptoms [ ]

	Visual Analog Scale (by parents if child < 5 years)
1. Provoking Factor(s)	0 ---------- 10
2. Flushing	0 ---------- 10
3. Diarrhea	0 ---------- 10
4. Pruritus	0 ---------- 10
5. Localized Bone Pain	0 ---------- 10

Scorma index: A/5 + 5B + 2C/5 [ ]



LOCAL SCORMA INDEX-FOR AREA(S) TREATED-Indicate Area(s) Treated

A. Extent: Percent/area of skin treated-INDICATE AREA(S) TREATED

B. Criteria:	Intensity	Intensity Items
1. Pigmentation	[ ]	0= Absent
2. Vesiculation	[ ]	1= Mild
3. Elevation	[ ]	2= Moderate
4. (+) Darier's sign	[ ]	3= Severe

C. Subjective Symptoms

	Visual Analog Scale
1. Provoking Factor(s)	0----------10
2. Flushing	0----------10
3. Diarrhea	0----------10
4. Pruritus	0----------10
5. Localized Bone Pain	0----------10

SCORMA INDEX: A/5 + 5B + 2C/5 [ ]

Clinical Response Assessment: Global SCORMA Assessment

Week	SCORMA	% Resolution	ASSESSMENT
0			
2			

Complete response:

Clinically significant SCORMA improvement in all 3 parameters of % skin involvement; activity or symptoms &/or
Resolution of 75% of cutaneous lesions

Near Complete response:

Clinically significant SCORMA improvement in two of 3 parameters of % skin involvement; activity or symptoms and/or
Resolution of >50% of cutaneous lesions

Partial Response:

Clinically significant SCORMA improvement in one 3 parameters of % skin involvement; activity or symptoms and/or
Resolution of >25% of cutaneous lesions

No response:

No significant SCORMA improvement in any of 3 parameters of % skin involvement; activity or symptoms and/or
Resolution of no cutaneous lesions.

Clinical Response Assessment: Local SCORMA Assessment

Week	SCORMA	% Resolution	ASSESSMENT
0			
2			

Complete response:

Clinically significant SCORMA improvement in all 3 parameters of % skin involvement; activity or symptoms &/or
Resolution of 75% of cutaneous lesions

Near Complete response:

Clinically significant SCORMA improvement in two of 3 parameters of % skin involvement; activity or symptoms and/or
Resolution of >50% of cutaneous lesions

Partial Response:

Clinically significant SCORMA improvement in one 3 parameters of % skin involvement; activity or symptoms and/or
Resolution of >25% of cutaneous lesions

No response:

No significant SCORMA improvement in any of 3 parameters of % skin involvement; activity or symptoms and/or
Resolution of no cutaneous lesions.

THESE QUESTIONS CONCERN THE SKIN CONDITION WHICH HAS BOTHERED YOU THE MOST DURING THE PAST WEEK

During the past week, how often have you been bothered by:	Never Bothered ↓						Always Bothered ↓
1. Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Your skin condition **burning** or **stinging** .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Your skin condition **being irritated** . . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. The **persistence / reoccurrence** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. **Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. The **appearance** of your skin condition. .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. **Frustration** about your skin condition . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. **Embarrassment** about your skin condition.	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. **Being annoyed** about your skin condition .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. **Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Your skin condition making it hard to **show affection**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. The effects of your skin condition on your **daily activities**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16. Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐