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VALCHLOR Therapy in Conjunction with Triamcinolone 0.1% Ointment for the Treatment of Contact Dermatitis in Subjects with Early Stage Cutaneous T-cell Lymphoma (Mechlorethamine Induced Dermatitis Avoidance Study (MIDAS))
Protocol# RSLMG-17.10

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V. July 11th, 2017

1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

To study the efficacy of Triamcinolone in reducing the adverse effects of Valchlor therapy, particularly contact dermatitis in subjects with early stage Mycosis Fungoides.

1.2. Background

Mechlorethamine hydrochloride, commonly known as nitrogen mustard, is an alkylating agent that induces apoptosis in malignant T-cells and possibly disrupts interactions between keratinocyte-Langerhan cell-T-cell interactions (1). This agent was first used in the late 1950's as a topical therapy for the treatment of Mycosis Fungoides (MF) (2,3). Initially, its use involved dissolving lyophilized mechlorethamine in water and painting it onto the skin (4). However, this use was limited due to high rates (67%) of cutaneous hypersensitivity which led to its compounding into an ointment (5). Although, this resulted in lower and tolerable rates of delayed type cutaneous hypersensitivity (10%), its shelf life remained low. Ointment based mechlorethamine only lasted about a week before it started decomposing (6). Consequently, mechlorethamine started being prepared in a quick-drying, greaseless gel (Valchlor) composed of 0.016% w/w mechlorethamine, a free radical inhibitor (butylated hydroxytoluene) and diethylene glycol monoethyl ether. This formulation increased permeability into and solubility within the top layer of the skin (stratum corneum) making it easier to apply. It also shortens the time of response to treatment about 16 weeks earlier than when the ointment is used (7). Valchlor was approved in 2013 for the treatment of IA and IB MF, but almost a quarter of the subjects enrolled in the study (22%) discontinued treatment due to adverse reactions (7).
The most common adverse reactions were associated with the skin or subcutaneous tissue disorders. Contact dermatitis was seen in 56% of the subjects treated with Valchlor and 23% of these were moderately severe to severe. Other adverse reactions included pruritus (20%), bacterial skin infections (11%), skin ulceration or blistering (6%), or skin hypopigmentation (5%). Together, these adverse events encompass 98% of all adverse events. Despite this, mechlorethamine is usually recommended as

a primary treatment option for CTCL, as complete responses to topical mechlorethamine in early stage MF is associated with a lower risk of disease progression (6,8,9). Increasing the probability of subjects achieving a response to Valchlor treatment and prevent them from switching therapies could be a possibility if skin adverse reactions are managed. This could be done with the use of topical corticosteroids.

Triamcinolone 0.1% ointment is an anti-inflammatory, anti-pruritic, topical corticosteroid with vasoconstrictive actions usually used to treat eczema, dermatitis, allergies, and rashes. It's mechanism of action involves inhibiting the production of cytokines that cause inflammation, such as IL-1 (10). In this study, we aim to look at the efficacy of Triamcinolone in reducing the adverse effects experienced by MF subjects treated with Valchlor, specifically contact dermatitis, pruritus, and skin ulceration or blistering.

2. STUDY DESIGN

2.1. Overview

This is a two-arm, open-label study that aims to compare the incidence and severity of the most common adverse reactions to Valchlor therapy when used with or without triamcinolone ointment 0.1% in early stage MF subjects (Stage IA and IB) for a period of 4 months.

2.2. Rationale for Study Design

This study consists of two different therapies administered concurrently to the same subject but on different, discrete, skin lesions. A minimum of 8 cm^2 will be chosen for each treatment arm (Valchlor only or Valchlor and Triamcinolone ointment 0.1%). Lesions must have similar characteristics (scaliness, erythema, hyper-(hypo-) pigmentation, elevation, and total size) and location, and must be representative of the disease. Lesions treated with different treatments should be at least 10 cm away from each lesion. Treatment length will consist of 4 months, as most of the adverse effects experienced in subjects treated with Valchlor happened within the first 2 weeks of treatment and up to 89% of these occurred within the first four months.

Primary Objective:

To determine if Triamcinolone 0.1% ointment significantly reduces the incidence of dermatitis on subjects eligible to start Valchlor therapy.

Secondary Objective:

To distinguish the nature of contact dermatitis (allergic or irritant) induced by Valchlor therapy through skin biopsies, patch testing, and the comparison of genetic variability in all T-cell clones form skin biopsies of subject who develop dermatitis vs baseline.

Exploratory Objectives:

To determine the severity of dermatitis among both treatment arms, if any.

To if there is any difference in pruritus and sleep disturbance caused by itch in lesions treated with Valchlor therapy and Triamcinolone compared to lesions that are treated with Valchlor only.

To determine rate and severity of ulceration and skin blistering, and rate of skin hyperpigmentation in both treatment groups.

To measure efficacy of Valchlor therapy with Triamcinolone compared to Valchlor in subjects with early stage MF.

Primary Endpoint:

Incidence (percentage) of dermatitis in lesions treated concurrently with Triamcinolone 0.1% ointment versus those that are not. Dermatitis will be defined as a finding of cutaneous inflammatory reaction occurring as a result of treatment. This will be assessed as a value of present or not present, and may be confirmed by biopsy of the specimen.

Secondary Endpoint:

The presence of allergic vs irritant dermatitis will be characterized through skin biopsies sent for pathological review, patch testing, and measuring the genetic variability of the T-cell clones through sequencing of the CD3 region of all T-cell clones found in skin biopsies collected at timepoints when contact dermatitis develop vs. those collected at baseline.

Exploratory endpoints:

SCORAD score differences between lesions treated with Valchlor and Triamcinolone versus lesions treated with Valchlor only for a period of 4 months.

To determine if there is any difference in pruritus and sleep disturbance caused by itch among lesions treated with Valchlor or Valchlor and Triamcinolone, measured as a composite score of pruritus in each individual lesion for each treatment arm over a period of 4 months.

To determine rate (%) and severity of ulceration and skin blistering, and rate of skin hyperpigmentation in both treatment groups over a period of 4 months.

Efficacy of Valchlor therapy with Triamcinolone compared to Valchlor over a period of 4 months using CAILS.

2.3. Rationale for Dosage

Valchlor and Triamcinolone 0.1% ointment will be administered as described in their packaged inserts.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) Number of Subjects:

Based on statistical analysis performed (Section 13.1), we will need 22 evaluable subjects in this study to have a statistically significant difference between both treatments. We may recruit up to 28 subjects in this study to account for retention rate.

b) Gender and Age of Subjects

Males and females of 18 years of age or older will be eligible to participate in this study.

c) Racial and Ethnic Origin:

All races and ethnicities will be recruited.

3.2. Inclusion and Exclusion Criteria

a) Inclusion Criteria:

- Be eligible to receive Valchlor therapy.
- Be at least of 18 years of age and ability to give informed consent
- Have stage IA or IB CTCL
- Subjects with histologic variants of Mycosis Fungoides such as folliculotropic, granulomatous slack skin, syringotropic MF, or large cell transformation are eligible.
- A skin biopsy within the last 60 days before start of treatment. In cases with equivocal histological features, the diagnosis may be confirmed with clinicopathologic and/or genetic testing consistent with the National Comprehensive Cancer Network guidelines for Mycosis Fungoides. If sufficient tissue is not available to perform genetic testing, a new biopsy will be performed even if the subject has had a biopsy within 60 days of start of treatment.
- Females of child bearing potential must agree to use two highly effective methods of contraception (strongly recommended that one of the two forms of contraception be non-hormonal such as condom plus spermicide, condom plus diaphragm with spermicide, or have a vasectomized partner) or use an intrauterine device until 30 days after the last day of drug administration. Perimenopausal women must be amenorrhoeic for at least 12 months to be considered of nonchildbearing potential.
- Males with female partners of child bearing potential must agree to sexual abstinence or use two reliable forms of effective contraception simultaneously (strongly recommended that one of the two forms should be non-hormonal as described above) during the entire treatment period and 30 days after the last dose.
- Must be able to comply with the study instructions, apply the study medication as directed, and attend all visits.

- Willingness to avoid sun exposure and UVB light in areas to be treated.

b) **Exclusion Criteria:**

- Have been treated with topical mechlorethamine within 6 months in lesions followed during this study.
- Have received any topical therapy directed against MF within 2 weeks of start of treatment in areas intended to be treated in this study.
- Have received any systemic therapy (oral or injectables) within 3 weeks of start of treatment.
- Not have any intercurrent illness or infection that would interfere with study participation
- Known hypersensitivity to mechlorethamine or triamcinolone.
- Breastfeeding, pregnancy, or intention to become pregnant.

3.3. Discussion of Subject Population

Inclusion and Exclusion Criteria are designed for a specific population who can receive the drug. While Valchlor is a topical agent and has not been detected systemically in prior studies when applied topically, fetal harm and malformations have been reported for systemic administration of mechlorethamine (11). Mechlorethamine was teratogenic and embryo-lethal after a single subcutaneous administration to animals. Therefore, adequate forms of contraception are described in the eligibility criteria and have excluded pregnancy or those who intend to become pregnant in this study.

Subjects must also have not obtained treatment that could blur the results of the study. Therefore, washout periods are essential and an adequate plan to exclude those who received potential therapies that could blur results need to be in place.

4. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

4.1. Method of Subject Identification and Recruitment

Subjects will be recruited through the site's clinic, through an principal investigator and/or investigator letter sent to physicians around the area for referrals, online advertisement, and flyers. All material that would directly reach to potential subjects must be approved by the ethical review board prior to distribution.

4.2. Process of Consent

Only individuals who are delegated authority by the PI are authorized to obtain consent. The process will be free of coercion and undue influence, and will provide enough information and sufficient time to be conducive to rational and thoughtful decision making by the subject. Subjects will be given a copy of the IRB approved informed consent at least 24 hours for review of the document, and will be encouraged to discuss this study with family and friends.

Subjects will then be walked through the consent form in a private room, be reminded that participation in this study is entirely voluntary, and his/her decision will not affect

the care which he/she is entitled in any way. Subjects can withdraw at any time.

The nature of the study, its purpose, the procedures involved, expectation of duration, potential risks and benefits, and any potential discomfort should be explained. The informed consent should be approved by the IRB and should be written in non-technical language.

The person obtaining consent will assess subject understanding before the consent form is signed and dated by the subject as well as make sure that all the subject's questions have been answered. No study related procedures can be made before consent is obtained.

5. METHODS AND STUDY PROCEDURES

The screening visit will be held 30 days or less prior to pre-treatment. From then onwards, visits will be held monthly, with unscheduled visits if necessary for up to four months.

The following procedures will be done at the following visits:

Screening Visit (30 days or less prior to baseline visit):

- Informed Consent
- Inclusion/Exclusion Criteria
- Measurement of vitals (weight, height, heart rate, blood pressure, and respiratory rate).
- Subjects will be put in to a gown for a CTCL physical examination
- Medical history and demographics (DOB, race, sex, ethnicity)
- Adverse event (AE) evaluation
- Review of concomitant medications
- Review of prior CTCL therapies
- Urine or Serum pregnancy test (females of child bearing potential only)
- Identification of potential lesions to be treated
- Two 3mm or one 6mm skin biopsy(-ies) will be performed if not done within 60 days of starting treatment for diagnostic and clone testing. Pathology read and immunohistochemistry will be performed on the sample. The skin biopsy must be taken from lesions that have not been treated topically for at least two weeks. Consequently, skin biopsies may happen at Screening or baseline visits including anytime between these visits.

<u>If subject meets enrollment criteria:</u>

Baseline visit (+/- 3 days):

- CTCL specific physical examination and vitals
- Photographs (individual lesions)
- CAILS assessment
- mSWAT
- VAS
- SCORAD assessment
- Physician Global Assessment

- Dispensing of drug and drug log
- AE assessment
- Review of concomitant medications
- A demo tube may be used to show subjects how to apply the drug at night
- A body map (as shown in Appendix 2) will be given to the subject with labeling on which treatment(s) goes on what lesions for compliance.
- Provide written instructions about administration and storage of investigational products
- Urine or serum pregnancy test (if needed)
- $50 compensation
- Skin Biopsy (if necessary)

Day 28 visit (+/- 3 days):

- Physical examination specific to study treatment plus vitals
- Photographs
- CAILS assessment
- mSWAT
- VAS
- SCORAD assessments
- Physician Global Assessment
- Dispensing of drug
- Drug accountability and compliance
- AE assessment
- Review of concomitant medications
- Skin biopsy (if needed for contact dermatitis)
- Urine or serum pregnancy test (if needed)
- $50 compensation

Months 2 and 3 (+/- 3 days):

- Physical examination specific to study treatment plus vitals
- Photographs
- CAILS assessment
- mSWAT
- VAS
- SCORAD assessment
- Physician Global Assessment
- Dispensing of drug
- Drug accountability and compliance
- AE assessment
- Review of concomitant medications
- Skin biopsy (if needed for contact dermatitis)
- Urine pregnancy test (if needed)
- $50 compensation

Month 4 (EOT, +/- 3 days):

- Physical examination specific to study treatment plus vitals
- Photographs
- CAILS assessment
- VAS
- mSWAT
- SCORAD assessment
- Physician Global Assessment
- Drug accountability and compliance
- AE assessment
- Review of concomitant medications
- Two 3mm skin biopsies of Valchlor only treated lesion (for H&E, and Immunoseq)
- Two 3mm skin biopsies of Valchlor and TAC lesion (for H&E and Immonoseq)
- Urine or serum pregnancy test (if needed)
- $50 compensation

Follow-up visit (Months 5 and 12 +/- 7 days after last dose):

- Physical Examination
- Vitals
- Photographs
- CAILS assessment
- mSWAT
- VAS
- SCORAD assessment
- Physician Global Assessment
- AEs assessment
- Review of concomitant medications
- $50 compensation
- Urine or serum pregnancy test (if needed)

Unscheduled visits might have any of the procedures mentioned above if PI determines them necessary. If clinical progression is noted at any time prior to the scheduled assessments for efficacy, CAILS and skin photographs, and any standard of care procedure that the PI seems appropriate, should be done at that time to fully document disease progression. If a biopsy is done for contact dermatitis, then some of this tissue will be sent for immunosequencing as well.

Patch Testing

If a subject develops dermatitis suspected to be due to mechlorethamine treatment, an optional patch testing of the subject may occur at any time during the study period. Standard patch testing is where a small concentration of mechlorethamine will be placed on the skin for approximately 48 hours. Clinical follow up occurs both when patches are removed from the skin (at approximately Day 2, 48 hours+/- 24 hours) and at Day 4, 96 hours (+/- 24 hours). General patch testing requires a visit on Days 0 (patches are placed and initial consultation), Day 2(patches removed and first

evaluation-early response), and Day 4(second evaluation-delayed response). Patch testing to mechlorethamine will be provided at varying concentrations. The subject will present for patch testing on a Monday (Day 0), Wednesday (Day 2), and Friday (Day 4) of one week. A skin biopsy sample will be collected for immunosequencing.

5.1. Treatment Dosage and Administration

This study consists of two different therapies administered concurrently to the same subject but on different, discrete, skin lesions.

A minimum of 8 cm^2 will be chosen for each treatment arm. Lesions treated with different treatments should be at least 10 cm away from each other.

Lesions must have similar characteristics (scaliness, erythema, hyper(hypo)pigmentation, elevation, and total size) as well as location. Lesions must be representative of the disease and not be in face, axillae, or intertriginous groin.

Treatment length will consist of 4 months, as most of the adverse effects experienced in subjects treated with Valchlor happened within the first 2 weeks of treatment and up to 89% of these occurred within the first four months.

Valchlor will be applied topically to affected areas at night. It must be applied at least 4 hours before or 30 minutes after showering or washing. Treated areas will need to dry for 10 minutes after application before covering with clothing.

Triamcinolone will be applied 30 min after taking a shower on a minimum of 8 cm^2 per treatment arm. Lesions treated with different treatments should be at least 10 cm away from each lesion.

Table 1. Regimen Description

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Valchlor	Keep refrigerated. Use immediately after removal from refrigerator or within 30minutes. Do not apply to face, axillae, or groin area Wash hands thoroughly after application.	0.016% w/w mechlorethamine gel	Topical	Every day at night	1 month
Triamcinolone	Apply on completely dry skin 30 minutes after washing/taking a shower.	0.1% ointment	Topical	Up to three times daily	

A body map will be given to the subject with areas labeled with each treatment assigned; to ensure he/she applies the correct drug on the correct lesion. Subjects will be instructed to report to the study staff if a mistake was made when applying either Valchlor or Triamcinolone.

Treatment with Valchlor will be stopped for any grade of skin ulceration, blistering, or moderately-severe or severe dermatitis (i.e. marked skin redness with edema).

Treatment limiting AEs will be grade 3 or 4 local dermal irritations that do not resolve to a grade 2 or lower within two weeks off the study drug.

Treatment frequency will be suspended or reduced for a maximum period of 4 weeks and resumed after irritation improves to a grade 2 or lower. Once AE improves, treatment can be restarted at a frequency of once every 3 days. After one week, and if dose is tolerated, dose will be increased every other day per week and then applied daily if drug is tolerated.

The use of corticosteroids for the treatment of skin irritation in lesions receiving only Valchlor is not accepted. Topical emollients or topical antihistamines are permitted.

Subjects with positive-patch test results (allergic contact dermatitis) associated with grade 3 or 4 reactions will be withdrawn from the study.

Triamcinolone will first be applied to select lesions in the morning, once daily and used up to three times daily if it helps tolerate any adverse reactions induced by Valchlor. Triamcinolone will not be used any more frequently than stated in the package insert. Treatment limiting AEs would be the development of striae, miliaria, and allergic contact dermatitis. These scenarios are rare. In the case of striae and miliaria, subjects will be dose reduced to three times a week. If an allergic contact dermatitis develops, the subjects will be removed from the study.

5.2. Efficacy Assessments

Evaluation of Skin Disease

Skin Biopsy

If histological diagnosis of CTCL has not been confirmed within 60 days of the Pre-treatment visit, a biopsy should be done if PI determines necessary. Subjects must have appropriate staging to meet study inclusion criteria. If not enough tissue is left over for immunosequencing, an additional biopsy will be required. The skin biopsy must be taken from lesions that have not been treated topically for at least two weeks. Consequently, skin biopsies may happen at Screening or baseline visits including anytime between these visits.

Subsequent biopsies to confirm a complete response, transformation of disease, disease progression, or skin rash/dermatitis can be performed at the discretion of the principal investigator and/or investigator.

Skin Biopsies for Clone Testing

Skin biopsies will help determine if malignant clones are present before and after treatment, and assess how these differ per treatment arm. This will be done in collaboration with Adaptive Biotechnologies (12).To profile the contact dermatitis, immunosequence of contact dermatitis skin samples will also be done. Left over DNA, protein, and tissue will be stored for future research with appropriate consent from subjects.

Skin Photographs

Lesions to be treated during this study will be selected at baseline. These will be measured and photographed using a digital camera dedicated for the study.

Skin photographs should be obtained prior to administration of study drug on Day 1 of the first treatment cycle and then as specified in the study procedures.

Special care should be taken to shield the subject's identity. Preference to lesions that are not within or close to tattoos should be given, if applicable. Pictures will then be modified to cover identifying tattoos or unique traits (if possible) if they result in a publication.

Composite Assessment of Index Lesion Severity (CAILS)

CAILS is an objective, quantitative, method to assess the extent of skin lesions. Skin lesions and erythema will be evaluated using CAILS (13). Two CAILS will be done, one for each treatment arm. An area of at least $8cm^2$ for each treatment arm will be compared. Lesions treated with different treatments should be at least 10cm away from each lesion.

Individual index lesion clinical signs and symptoms will be graded at each visit according to the scales found in Tables 2 and 3. A Composite Assessment will be generated for each time point by a summation of the grades for each index lesion erythema, scaling, plaque elevation, hypopigmentation or hyperpigmentation, and area of involvement. The index lesion grade at baseline will be divided into the grade at each subsequent study visit to determine the subject's response to treatment. Any ratio of the grade obtained at the visit vs. the one obtained at baseline that is >1.0 will indicate worsening of disease.

Based upon the ratio and the absence or presence of other disease manifestations, the CTCL response to treatment according to the composite assessment endpoint will be classified by the best to worst response hierarchy of CR, PR, SD, or PD, with the exception that if PD precedes a better response (CR, PR, or SD) the subject will be classified as PD, even if the subject meets response criteria subsequent to the progressive disease. Confirmation by at least two assessments separated by at least four study weeks is required for a partial or complete response classification. If a PR or CR is achieved prior to a PD, and subject then meets PD criteria, these will be considered a relapse.

The evaluations of index lesions should be made with non-leading (non-directive) questions of symptoms to the subject. Examples of symptom-related events should be elicited from the subject to substantiate grading severity. Observations of index lesion clinical signs and determination of the index lesion areas should be made with the subject as fully undressed as necessary to evaluate all index lesion areas.

To determine the area of index lesions, the longest diameter and the longest diameter perpendicular to this diameter of each index lesion will be measured to the nearest millimeter. The lesion area will be the product of these two diameters and then graded as in Table 2. If there is central clearing of an index lesion (clearing of disease within the outer boundaries of the lesion), then the product of the largest perpendicular diameters of the area(s) of clearing will be subtracted from the area determined from the outer boundary diameters before assigning the appropriate grade as in Table 2.

Table 2. Grading Scales for Composite Assessment of Index Lesion Clinical Signs

Lesion Type	Abnormal Skin
Scaling	0 No evidence of scaling on the lesion 1[a] 2 Mild: Mainly fine scales; lesion partially covered 3[a] 4 Moderate: Somewhat coarse scales; lesion partially covered; rough surface 5[a] 6 Severe: Coarse, thick scales, virtually all of the lesion covered, rough surface. 7[a] 8 Very severe: Coarse, very thick scales; all of the lesion covered; very rough surface
Erythema	0 No evidence of erythema, possible brown hyperpigmentation 1[a] 2 Mild: Light red lesion 3[a] 4 Moderate: Red Lesion 5[a] 6 Severe: Very Red Lesion 7[a] 8 Very severe: Extremely Red Lesion
Plaque/Tumor Elevation	0 0mm: No evidence of plaque above normal skin level 1[a] ≥0 to <0.5mm: minimal but definite plaque elevation above normal skin level 2 ≥0.5 to <1mm: Slight but definite plaque elevation 3[a] ≥1 to <1.5mm: Mild Elevation 4 ≥1.5 to <2mm: Moderate Elevation 5[a] ≥2 to <2.5mm: Moderate to Marked Elevation 6 ≥2.5 to < 3mm: Marked Elevation 7[a] ≥3 to < 3.5mm: Very marked elevation 8 ≥3.5mm: Extreme elevation
Index Lesion	0 0 cm2 (no measurable area)

Area	1 > 0 and ≤ 4 cm2 2 > 4 and ≤ 10 cm2 3 >10 and ≤ 16 cm2 4 >16 and ≤ 25 cm2 5 >25 and ≤ 35 cm2 6 >35 and ≤ 45 cm2 7 >45 and ≤ 55 cm2 8 > 55 and ≤ 70 cm2 9 >70 and ≤ 90 cm2 10 >90 and ≤ 110 cm2 11 >110 and ≤ 130 cm2 12 >130 and ≤ 155 cm2 13 >155 and ≤ 180 cm2 14 >180 and ≤ 210 cm2 15 >210 and ≤ 240 cm2 16 >240 and ≤ 270 cm2 17 >270 and ≤ 300 cm2 18 >300 cm2

a Intermediate intervals 1, 3, 5 and 7 are to serve as mid-points between the defined Grades 0, 2, 4, 6 and 8.

Table 3. Response Criteria for Skin

Response	Description
Complete Response (CR)	CA ratio = 0, no clinically abnormal lymph nodes (and no cutaneous tumors, or known pathologically positive lymph nodes or visceral disease, or other tumor manifestations) are found, and a cutaneous biopsy documenting absence of histologic signs of CTCL from a cleared lesion is obtained
Partial Response (PR)	If the CA ratio is ≤ 0.5 and there is a < 25% increase in the number or aggregate area of clinically abnormal lymph nodes, cutaneous tumors, or known pathologically abnormal lymph nodes or visceral disease; and no new pathologically abnormal lymph nodes or new visceral disease in a location where prior evaluation for disease documents the absence of disease within 30 days of entry in the study
Stable Disease (SD)	If none of the other response classifications (i.e., CR, PR, or PD) accurately describe the disease status, then the response classification is SD.

Progressive Disease (PD)	If the CA ratio is ≥ 1.25, or there is a ≥ 25% increase in the discrete number of or aggregate area of clinically abnormal lymph nodes, cutaneous tumors, known pathologically abnormal lymph nodes or known visceral disease; or a new cutaneous tumor or new pathologically positive lymph node or new visceral disease in an area documented to be free of disease within 30 days of entry in the study

Modified Skin Weighted Assessment Tool (mSWAT):

The mSWAT will be used to quantify overall disease involvement in the whole body. This tool uses the total area of skin involved based on the body surface area. Lesions are weighted by lesion characteristic (patch, plaque, and tumor).

Table 4. mSWAT

Body region (%BSA)	Patch*	Plaque*	Tumor*
Head (7 %)			
Neck (2%)			
Anterior trunk (13%)			
Arms (8%)			
Forearms (6%)			
Hands (5%)			
Posterior trunk (13%)			
Buttocks (5%)			
Thighs (19%)			
Legs (14%)			
Feet (7%)			
Groin (1%)			
Subtotal of lesion BSA			
Weighting factor	x1	x2	x4
Subtotal lesion BSA x weighting factor			
mSWAT score = summation of each column line above =			

patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present.

plaque = any size lesion that is elevated or indurated; crusting, ulceration or poikiloderma may be present.

tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Subjects will be monitored for overall disease burden throughout the study for safety. The following response criteria as assessed by mSWAT will be followed:

Table 5. Response, as assessed by mSWAT

Response	Definition
CCR	100% clearance of skin
PR	50 to 99% clearance of skin disease from baseline without new tumors (T3) in subjects with T1, T2, T4 only skin disease
SD	<25% increase to <50 clearance in skin disease from baseline without new tumors (T3) in subjects with T1, T2, or T4 only skin disease
PD	≥25% increase in skin disease from baseline or development of new tumors in those with T1, T2, T4 only skin disease, or loss of response: in those with a CR or PR, increase of skin score of greater than the sum of the nadir plus 50% baseline score.
Relapse	Any disease recurrence in those with a CR

SCORAD (SCORing Atopic Dermatitis) tool

The extent of dermatitis on subjects will be measured using SCORAD. This tool will be used to determine the severity of the dermatitis.

Given that only specific lesions on the body of each subject will be treated, we will consider a maximum score of 100% if the total body surface area treated by specific treatment is covered by dermatitis. This will be determined by calculating the percentage of skin that is covered by dermatitis depending on surface area. This will be score “A”.

The intensity criteria are met by scoring Erythema, Edema/papulation, oozing/crusting, excoriation (scratch marks), xerosis (dryness), and thickness on a scare of 0-3 (0=None, 1=Mild, 2=Moderate, 3=Severe). A lesion that is representative of most of the subject's dermatitis should be chosen (not the worst or the best-looking lesion). Xerosis must be scored on an area of skin without inflammation.

These are then added up to give a total score of “B”.

Subjective symptoms of pruritus and insomnia are then scored using visual analog scales that run from 0-10 (0=none, 10= worst imaginable).

These are then added up to give a total score of “C”.

To calculate the final score the following equation is used:

Final score = A/5 + 7B/2 + C

The lowest possible score would be zero and the highest 103. Scored will be graded as outlined on table 6 below.

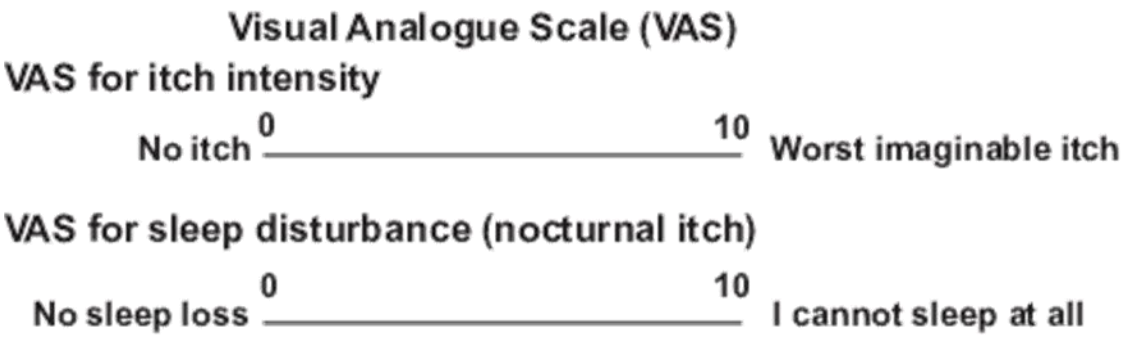
Table 6. SCORAD Score and Severity of Dermatitis Evaluation

Severity of Dermatitis	Score
Mild	<25
Moderate	25-50
Severe	>50

Pruritus and Insomnia Evaluation

A visual analog scale for each treatment arm will be done at each timepoint. Subjects will be asked what their overall itchiness is in the lesions receiving specific treatment (Valchlor only vs Valchlor and Triamcinolone).

Figure 1. Grading Scale for Index Lesion Pruritus and Insomnia.



Subjects will be instructed to draw a line anywhere along the lines of the VAS scales to indicate severity of itch and sleep disturbance. A VAS score for itch intensity will be obtained for each lesion treated and summed up.

Physician Global Assessment:

The physician global assessment (PGA) represents the principal investigator and/or investigator's overall assessment of the extent of improvement or worsening of the subject's cutaneous disease compared with baseline as shown in table 7. This assessment is designed to consider all cutaneous lesions, including index and non-index lesions.

Table 7. PGA

Grade	Description	Response
0 completely clear	No evidence of disease; 100% improvement	CCR
1 almost clear	Very obvious improvement (≥90% to <100%); only traces of disease remain	PR
2 marked improvement	Significant improvement (≥50% to <90% clear); some of disease remains	
3 moderate improvement	Intermediate between marked and mild (≥25% to <50%)	
4 slight improvement	≥10% to , 25%; significant evidence of disease remains	Stable
5 no change	Disease has not changed significantly from baseline (10 to -25%)	
6 condition worse	Disease is worse than baseline by ≥25%	PD

5.3. Safety Assessments

Physical exams, vitals, and CTCL assessments will assess subject safety throughout the study. AEs and concomitant medications will be assessed at each subject visit. Subjects will be instructed to call to schedule an unscheduled visit if they have pertinent problems that cannot wait within the four scheduled visits. Principal investigator and/or investigator will determine if subject needs to come in for an unscheduled visit for safety.

5.4. Assessment of Subject Compliance

Compliance to study medication will be measured through follow up with a drug log. Subjects will be given a log to record each application. This log will be reviewed at each scheduled visit.

5.5. Costs to the Subject

Study subjects will not be charged for procedures that are performed solely for research purposes such as CTCL and contact dermatitis specific assessments (CAILS, SCORAD, photographs, etc), and immunosequencing. Triamcinolone and Valchlor will be supplied to subject at no cost. Subjects will be ultimately responsible for diagnostic tests, and assessments that would otherwise be performed had the subject not been in a research study. Such procedures are considered standard of care.

5.6. Payment for Participation

Subjects will receive a compensation of $50.00 per completed visit.

5.7. Return of Individual Research Results

Subjects will not be notified about results of the study. However, a publication at the end of the study is expected that will show the results of the study. No personal identifying information will be used in publications.

6. CONCOMITANT AND DISALLOWED MEDICATIONS

The following medications are prohibited:

- Any therapy against MF other than the one administered during this study on the lesions being evaluated
- Sun light or UVB exposure on lesions evaluated
- Subjects may receive other topical treatments in lesions not being followed for this study as long as they do not have any systemic effects.
- The use of systemic steroids
- Alternative medications, particularly, St. John's wort.

7. SUBJECT WITHDRAWALS

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. Subjects might be withdrawn from the study at discretion of the principal investigator and/or investigator if he determines it is in the subject's best interest to discontinue treatment. Subjects may also be withdrawn from the research activities if there is subject non-compliance, worsening of disease, intercurrent illness, or pregnancy.

Subjects will not be replaced and data collected with be used in the analysis unless subject revokes consent via written form.

8. STUDY DRUG/DEVICE/BIOLOGIC ADMINISTRATION/ASSIGNMENT

8.1. Study Drug/Device/Biologic

Valchlor (please see package insert attached) and Triamcinolone 0.1% ointment (package insert also attached).

8.2. Dosage of Study Drug/Biologic

Valchlor will be applied topically every day for 4 months unless instructed otherwise. Triamcinolone will be applied topically every day for 4 months, up to three times daily. Please refer to section 5.1 for details on dose interruptions and reductions.

8.3. Accountability of Investigational Supplies

Drugs will be stored as described in their package inserts:

Valchlor will be kept refrigerated at temperatures between 2-8°C.

Triamcinolone will be kept at room temperature (15-30°C).

8.4. Subject Withdrawal of Study Drug

Please refer to section 5.1 for details on dose interruptions and reductions.

9. SAFETY AND REPORTABLE EVENTS

9.1. Adverse Event Definition

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal lab finding), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Each AE must be assessed by the principal investigator and/or investigators as to whether or not there is a reasonable possibility of causal relationship to Valchlor, and documented as either related or unrelated. The determination of the likelihood that Valchlor caused the AE must be provided by an investigator who is a qualified physician.

9.2. Serious Adverse Event

A serious adverse event is defined as any adverse medical experience that results in any of the following outcomes:

- Death;
- Life threatening
- Hospitalization
- Inpatient new or prolongation of existing hospitalization;
- Disability/incapacity
- Is a congenital anomaly/birth defect, or
- Requires medical or surgical intervention to prevent permanent impairment or damage.

9.3. Recording Adverse Events

The NCI-CTCAE v4.0 system will be used to grade AEs, both clinical and laboratory. AEs will be grouped and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms by system organ class. All subjects will be assessed regularly for potential occurrence of AEs from the time following the first dose of study drug until 30 days after the last dose or initiation of alternative therapy whichever comes first.

The principal investigator and/or investigator will inquire about AEs at all subject visits by asking the subject a question such as: “How have you been feeling since your last visit?” All AEs, whether observed by the principal investigator and/or investigator or reported by the subject, must be collected and recorded on the appropriate AE page of the CRF and as appropriate on the SAE form. The collection of AE information commences following the subject’s written Informed Consent to participate in the study. If a subject experiences an AE, the subject will receive appropriate treatment and supportive care as necessary, and the principal investigator and/or Investigator will continue to follow up

until there is a return to the subject's baseline condition, or until a clinically satisfactory resolution is achieved.

Timely and complete reporting of all AEs will aid in identifying any untoward medical occurrence, thereby allowing: (1) protection of safety of study subjects; (2) a greater understanding of the overall safety profile of the study drug; (3) recognition of dose-related study drug toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to worldwide regulatory requirements.

All adverse events, whether observed by the principal investigator and/or Investigator, elicited from or volunteered by the subject, should be documented. Each adverse event will include a brief description of the experience if no term is available for it, the date of onset, the date of resolution, the duration and type of experience, the severity, the relationship to investigational products, contributing factors, and any action taken with respect to the study drug/device.

Standard medical terminology should be used to document AEs on the CRF. The subject's exact description of the event will be recorded in the source documentation. In the case of signs and symptoms, the underlying illness or diagnosis will be recorded as the event when known.

All AEs will be graded using CTCAE Version 4.0 as described in Table 8 below:

Table 8. AE Grading Criteria

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not Indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADLa
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADLb
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

a: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
ADL = Activities of Daily Living

For AEs not contained within CTCAE, Version 4.0, the principal investigator and/or Investigator will assess the severity/grade of an AE according to the five grades above.

Adverse Event Relationship to Study Drug:

The relationship of each AE to the study drug will be evaluated using the following guidelines:

Related

This category applies to any AE (whether serious or not) that appears to have a reasonable possibility to the use of Valchlor (i.e., a relationship cannot be ruled out). Guidelines to determine whether an event might be considered related include (but are not limited to) the following:

1. There is a temporal relationship between the occurrence of the event and the administration of Valchlor.
2. The event abated (diminished) or disappeared when treatment with Valchlor was down-titrated, interrupted, or discontinued.
3. Positive results in a drug sensititvity test (skin test, etc).
4. Toxic level of the drug as evidenced by measurement of drug concentrations in blood or other bodily fluid.

Not Related

An AE (whether serious or not) that does not follow a reasonable temporal sequence from administration of the drug or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

9.4. Responsibilities for Reporting Serious Adverse Events

Principal investigator and/or investigator will conduct continuous review of data and subject safety. The review will include for each treatment arm: the number of subjects enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed. The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required complications, or sequelae.

- Principal investigator and/or investigators are to report the following information items to the IRB within 5 days:
    - New or increased risk. For example, publications indicating a new risk, new risk in an investigator brochure, FDA black box warning, new risk identified in a data safety monitoring report, information or change that adversely affects subject safety, or information or change that adversely affects the conduct of the research.
    - Protocol deviation that harmed a subject or placed subject at risk of harm
    - Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
    - Audit, inspection, or inquiry by a federal agency
    - Written reports of federal agencies (e.g., FDA Form 483)
    - Allegation of Noncompliance or Finding of Noncompliance
    - Unauthorized disclosure of confidential information
    - Unresolved subject complaint
    - Suspension or premature termination by the sponsor, principal investigator and/or investigator, or institution

- Incarceration of a subject in a research study not approved to involve prisoners
- Adverse events or IND safety reports that require a change to the protocol or consent
- State medical board actions
- Information where the sponsor requires prompt reporting to the IRB

- Fatal serious adverse events will be reported within 24 hours of knowledge to Actelion. Actelion will expedite reports to the FDA and other regulatory authorities as appropriate per local and international regulatory reporting requirements.
-

- SAEs that are related and unexpected to the investigational products used in this protocol will be reported to the sponsor, IRB, and/or other applicable authorities.

- All SAEs that are possibly related to the study medication by the Sponsor-Principal investigator and/or investigator, must be reported immediately to Actelion Global Drug Safety (GDS) as set forth in the IIS agreement and within 24 hours of knowledge of the event. Actelion reserves the right to request additional information and clarifications on cases forwarded by the Sponsor-Principal investigator and/or investigator. SAE forms should be sent the the following e-mail or fax number:

  North America (US and Canada)
  San Francisco, USA
  DrugSafetyUS@actelion.com
  Fax: 1-866-227-5886

  The principal investigator and/or investigator is obligated to immediately report any SAE occurring at any time after the subject signs the Informed Consent Form and all unresolved adverse events should be followed by the sponsor-principal investigator and/or investigator 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 sponsor-principal investigator and/or investigator should instruct each subject to report, to the sponsor-principal investigator and/or investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

9.5. Pregnancy Reporting

Any pregnancy occurring during the course of the study, up until 30 days after discontinuation of therapy will be reported within 24 hours of the Investigator's knowledge to the Sponsor and regulatory authorities if applicable. Pregnancies will be reported using the Actelion Pregnancy Form (Appendix 4) to the following email or fax:

DrugSafetyUS@actelion.com
Fax: 1-866-227-5886

Any pregnancy will be followed until its conclusion and its outcome will be reported to the sponsor and regulatory authorities if applicable.

10. RISK/BENEFIT ASSESSMENT

10.1. Potential Risks

Valchlor risks:

- Flammable Gel
- Embryo-fetal Toxicity
- Dermatitis
- Non-melanoma skin cancer
- Mucosal or eye injury
- Secondary exposure to Valchlor

Reported in more than or equal to 5% of subjects:

- Dermatitis
- Pruritus
- Bacterial skin infection
- Hematological abnormalities (decreased hemoglobin, neutrophils, or platelets).

Triamcinolone 0.1% ointment Risks:

Triamcinolone Acetonide 0.1% Ointment Risks:

Infrequent reactions to topical corticosteroids that occur more frequently if an occlusive dressing is used (listed in decreasing order of frequency):

- Burning
- Itching
- Irritation
- Dryness
- Folliculitis
- Hypertrichosis
- Acneiform eruption
- Hypopigmentation
- Perioral dermatitis
- Allergic contact dermatitis
- Skin maceration
- Secondary skin infection
- Skin atrophy
- Striae
- Miliaria

Other risks if systemic absorption:

- HPA axis suppression
- metabolic effects (hypoglycemia, hypokalemia)

10.2. Protection Against Risks

Subjects will be followed up after each procedure to ensure safety. Principal investigator and/or investigators will pay attention to changes from baseline and use standard techniques for skin biopsies and other procedures done. The subject will assume responsibility for payment for the treatment of all adverse events.

10.3. Potential Benefits to Subjects

Response to treatment with clearance of disease is possible but uncertain.

10.4. Alternatives to Participation

Available skin-directed therapies such as topical glucocorticoids, carmustine (BCNU), psoralen plus ultraviolet-A radiation (PUVA) and electron beam radiation therapy (EBT) can improve skin manifestations and induce temporary remissions.

Systemic therapies, such as bexarotene, denileukin diftitox injection, photopheresis, systemic mechorethamine, cyclophosphamide, vorinostat and methotrexate are typically targeted towards advanced stages of CTCL due to their greater potential for toxicity. Various treatments have also been used in combination.

11. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

Confidentiality is the ethical and/or legal right that information, such as research data, will be held secret and safeguarded from disclosure unless consent is provided permitting disclosure. Informed consent will include HIPAA authorization verbiage.

Upon enrollment, each subject will be assigned a unique subject number (UPN) that includes the study number at the front and a three-letter code. These will be used instead of their names whenever possible, such as when filling in study records. The master log that will link these codes with the names of each subject will be stored in a locked cabinet within a locked office. Case report forms and dedicated study camera will be kept in a locked cabinet within a locked office under control of PI and study staff delegated authority to take photographs. Case report forms will be kept within a locked cabinet in a locked office. Photographs obtained will be stored without any personal identifiers in them, except for a three-letter code and number assigned to each subject at the start of the study. Only the PI can grant permission to research staff to access this data.

12. RESEARCH INFORMATION IN MEDICAL RECORDS

Pathology reports will be stored in the medical record. A note stating that the subject is a participant of the study will also be placed on the record.

13. DATA ANALYSIS AND MONITORING

13.1. Planned Statistical Analysis

Using Fisher's exact test, we determined that we will need 22 evaluable subjects to get an 83% chance of detecting a significant difference at a two-sided 0.05 significance level. This assumes that 90% of subjects treated with Valchlor along with triamcinolone and 44% of those treated with Valchlor only will not get contact dermatitis. This calculation takes into account that 89% of subjects experience AEs in a period of 4 months when they are on VALCHLOR therapy.

To look at estimation of response rates for each treatment group: previous data suggests that the overall response for Valchlor is 50%. From our experience, the response rate for Valchlor plus triamcinolone is about 70%. With 22 subjects per group the 95% confidence intervals for the response rates would be expected to have widths of 44% for Valchlor (expected CI: 28% - 72%) and 41% for Valchlor plus triamcinolone (expected CI: 45% - 86%). These calculations are based on exact binomial Clopper-Pearson confidence intervals.

To account for retention rate, up to 28 subjects may be enrolled in this study.

13.2. Data and Safety Monitoring

Study principal investigator and/or investigators will conduct continuous review of subject accrual, eligibility, data collection, and subject safety. Study progress and safety will be reviewed in a quarterly basis. All AEs and SAEs that have occurred in the prior three months will be reviewed by writing all AEs and SAEs in a cumulative spreadsheet listing of all events submitted. A progress report will be written as well. AEs and SAEs will be reviewed in order to confirm toxicity grade, expectedness, relatedness, sequelae, follow up required, and risk to subjects.

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Appendix 1 Schedule of Activities

Visit	0 (Screening)	Day 1	Day 1(Patch Testing)	Day 2 (Patch Testing)	Day 4 (Patch Testing)	Day 28	Months 2 and 3	EoT	Follow up (5 and 12 months)
Visit Window	-30 days	+/- 3days				+/- 3days	+/- 3days	+/- 3days	+/- 3 days
Obtain informed consent	X								
Inclusion and exclusion criteria/Enroll	X								
Medical history and demographics	X								
Physical Examination	X	X				X	X	X	X
Vital signs	X	X				X	X	X	X
Skin Biopsy (including Pathology read and immunohistochemistry)	X[a]	X[a]	X			X[a]	X[a]	X[ba]	
CAILS + SCORAD+ mSWAT		X				X	X	X	X
PGA		X				X	X	X	X
Identification of lesions	X	X							
Pregnancy Test	X	X				X[c]	X[c]	X[c]	X[c]
Study drug dispensing		X				X	X		
Study drug Accountability						X	X	X	
Photographs		X				X	X	X	X
Adverse event review	X	X				X	X	X	X
Immunosequencing		X	X			X	X	X	
Concomitant Medications	X	X				X	X	X	X
Patch Testing	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	
Training on how to apply drug		X							
Subject Reimbursement	X	X		X	X	X	X	X	X

a) If PI determines necessary or PRN for contact dermatitis
b) A total of 2 skin biopsies per treatment arm will be done at the EOT visit. One for pathological review and the other one for immunosequencing.
c) If PI determines it is necessary

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Appendix II. Body Map