Valchlor in the Treatment of Lichen Planopilaris: A Single Arm, Open-label, Exploratory Study

NCT# NCT03417141

11/26/2018

VALCHLOR IN THE TREATMENT OF LICHEN PLANOPILARIS: A SINGLE ARM, OPEN-LABEL, EXPLORATORY STUDY

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Study Product: *VALCHLOR® gel*

Protocol Number: (IRBe) 16-006731

IND Number: *136907-Exempt from IND Regulations*

Final version:	**V7: 26 NOV 2018**	Increase of accrual
	V6: 05 OCT 2018	Change to drug application schedule, change to the number of drug tubes dispensed at baseline
	V5: 02 MAY 2018	Addition of hair count assessments
	V4: 06 MAR 2018	Overall study duration changed from calendar dates to length of time of patient exposure
	V3: 22 FEB 2018	Pp 21-24; AE definitions clarified and reporting of SAEs to Actelion added
	V2: 15 SEP 2017	Clarified Post IRB reviewed version; contraception requirements for females updated
	V1: 08AUG2017	Initial protocol

Table of Contents

List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
LPP	Lichen Planopilaris
FAA	Frontal Fibrosing Alopecia
MF	Mycosis Fungoides

Study Summary

Title	Valchlor in the Treatment of Lichen Planopilaris: A Single Arm, Open-Label, Exploratory Study
Running Title	Valchlor in the treatment of Lichen Planopilaris
Protocol Number	16-006731
Phase	Pilot Study
Methodology	Open-Label, Exploratory Study
Overall Study Duration	14 Months
Subject Participation Duration	6 months
Single or Multi-Site	Single
Objectives	To investigate the efficacy of Valchlor in the treatment of LPP.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Adults patient with active LPP or FFA 1) 18 years old or older at time of consent 2) Biopsy proven diagnosis of LPP or FAA
Study Product, Dose, Route, Regimen	Valchlor gel, average use one 60 gram tube per month
Duration of Administration	6 months
Reference therapy	Valchlor gel
Statistical Methodology	The primary endpoint for this study is the LPPAI score. While a minimal clinically significant difference for this outcome measure has not been established, clinically meaningful treatment responses will generate large changes in the LPPAI score given the weightings used in the underlying formula. Therefore, the proposed accrual target of twenty patients will be adequate for the preliminary data generating purposes of an exploratory study.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the protocol, Good Clinical Practice standards, and applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Lichen Planopilaris (LPP) is a form of lymphocyte mediated scarring alopecia. It is a chronic condition that predominates in women between the ages of 45-70. Patients present with discrete patches of hair loss with characteristic perifollicular erythema and scale [1]. Diffuse or localized scalp involvement may be seen. Disease progression results in irreversible hair loss and has been associated with significant impact on quality of life, depression, and anxiety [2]. Successful treatment of LPP requires clearance of the lymphocytic inflammation early in the disease course to prevent irreversible follicular destruction and permanent hair loss.

Conventional topical (e.g. corticosteroids) and systemic immunosuppressives (e.g. mycophenolate mofetil) used in the treatment of LPP directly inhibit lymphocytes but generally cannot induce clinical remission [3]. Therefore, there remains a critical unmet therapeutic need for an alternative topical product to treat LPP.

1.2 Investigational Agent

Valchlor, a gel formulation of mechlorethamine, is an alkylating agent with anti-neoplastic and anti-inflammatory properties. Each tube of Valchlor contains 0.016% of mechlorethamine which is equivalent to 0.02% mechlorethamine HCL. It is designed for topical application to non-mucosal skin surfaces. With topical administration, there is no systemic absorption. Valchlor is FDA approved for the topical treatment of Stage IA and IB mycosis fungoides (MF) type cutaneous T cell lymphoma in patients who have received prior skin-directed therapy.

1.3 Preclinical Data

Valchlor induces lymphocyte apoptosis through either direct cytotoxic effects or possibly through indirect alterations of the surrounding cytokine milieu. This has been demonstrated for neoplastic conditions such as mycosis fungoides as well as for other inflammatory skin disorders such as psoriasis [4,5]. Histologically, the lymphocytic inflammation in LPP is confined to the upper portion of the hair follicle known as the infundibulum. The superficial nature of this lymphocytic inflammation is ideally suited to targeted topical treatment and is also compatible with the absorption and penetration kinetics of Valchlor. The gel vehicle of Valchlor is also especially ideal for hair bearing scalp application. The distribution of Langerhans cells in the hair follicle is greatest in the infundibulum which also corresponds to where the lymphocytic inflammation in LPP is the greatest [6]. Valchlor has been shown to deplete resident Langerhans cells in the epidermis and has been previously reported to clear cutaneous lesions in Langerhans cell histiocytosis [7]. The failure of other systemic immunosuppressives in treating LPP may

reflect the fact that none of these agents directly target Langerhans cells, which constitute the main resident population of antigen presenting cells in both the epidermis and hair follicles and likely are a relevant therapeutic target in the treatment of LPP. Therefore, the multifactorial effects of lymphocyte depletion, Langerhans cell death, and cytokine expression alteration induced by Valchlor warrant investigation of the therapeutic potential of Valchlor in the management of LPP.

1.4 Clinical Data to Date

There is no clinical research data regarding the efficacy of Valchlor in the treatment of LPP.

1.5 Dose Rationale

The lymphocyte depleting properties of mechlorethamine, the active ingredient of Valchlor, have been clinically demonstrated with once daily application in the treatment of other skin disorders. The gel delivery vehicle produces immediate liquefaction and rapid drying upon contact which is ideal in the hair bearing scalp and helps to ensure application is restricted to the applied area.

1.6 Risks and Benefits

The postulated benefits of Valchlor include immunomodulatory effects to induce clinical remission through local effects on lymphocyte proliferation and Langerhans cell function. These benefits will occur without the toxicities associated with systemic immunosuppression, and without the dose-limiting effect of epidermal and dermal atrophy seen with daily high potency topical corticosteroid use.

The possible risks associated with Valchlor include:
1. Flammable Gel. The gel formulation is an alcohol-based product and is flammable when exposed to fire or other flame before completely drying. This risk will be minimized through application instruction procedures provided to study participants and the exclusion of smokers in the study.

2. Embryo-fetal Toxicity. Toxicity has been demonstrated with systemic administration of mechlorethamine, the active ingredient of Valchlor gel. This risk is minimized in that topical application of Valchlor is not associated with detectable levels systemic absorption. Additionally, pregnant, nursing females, or females planning or actively trying to become pregnant will be excluded from the study. All female study participants of child bearing potential prior will be screened for pregnancy with urine B-HCG testing at all study visits and will be required to use one form of contraception during the study period.

3. Non-Melanoma Skin Cancer. Retrospective analysis has shown that 2% (3/128) of patients receiving Valchlor for the treatment of early stage MF developed non-melanoma skin cancer after one year of use. Many of these patients had previously received other treatments known to increase skin cancer risk, and thus the absolute risk directly attributable to Valchlor has not been established. This risk will be minimized in this study in that patients will have surveillance skin

screening at each follow-up visits, a shorter 6 month treatment interval, and once daily application versus the BID to TID application utilized in patients with MF.

4. Mucosal or Eye Injury**.** Mechlorethamine, the active ingredient in Valchlor, can cause pain, burns, inflammation, photophobia, and blurred vision. Blindness and severe irreversible anterior eye injury may also occur. These risks are highly dependent on both the mechlorethamine concentration and delivery vehicle. For this study, the Valchlor formulation of mechlorethamine at 0.016% in a gel vehicle would be expected to be result in mild irritant reactions characterized by erythema or tearing in cases of accidental ocular and/or mucosal exposure. The concentrations producing scarring conjunctivitis or skin vesiculation have been reported to be 1% or higher and are far outside the range of concentrations used for medical purposes [8, 9]. Additionally, there are no reports in the indexed PubMed literature of mucosal blistering, cutaneous blistering/scarring, or permanent ocular injury including blindness with medical range concentrations of Mechlorethamine. Mechlorethamine is used in clinical practice in the United States for face and scalp site application. In mycosis fungoides, especially the folliculotropic variant, multiple case reports have described the use of mechlorethamine application to the face and scalp either as a single agent or in combination with high potency corticosteroids with excellent tolerability and no adverse mucosal or ocular events [10]. Mechlorethamine application to the scalp for Langerhans histiocytosis has also been reported as safe and effective in both the pediatric and adult literature [11]. The risk of the mucosal/eye injury is minimized in this study given the low concentration of Mechlorethamine utilized; additionally, study participants must demonstrate understanding and have the functional capacity to apply the topical Valchlor as directed to be enrolled in the study.

5. Dermatitis. Mechlorethamine in liquid, ointment, cream, and gel formation can induce an idiosyncratic contact dermatitis producing erythema, pruritus, and scaling to areas of application. This is highly treatment responsive to topical corticosteroids and resolves with discontinuation of topical application. This risk is minimized in that Valchlor with a gel vehicle has the lowest incidence of contact dermatitis of any medical grade formulation and that discontinuation of the Valchlor use also results in resolution of the dermatitis.

2 Study Objectives

The primary objective of this study is to assess the potential effectiveness of once daily application of Valchlor in decreasing disease activity in patients with Lichen Planopilaris. The primary measurement of efficacy will be with the Lichen Planopilaris Activity Index (LPPAI) before and after 6 months of treatment. Secondary measures of efficacy will be the mean follicular density, Physician Global assessment (PGA) score, and the Dermatology Quality of Life Index (DQLI) score before and after six months of therapy.

3 Study Design

3.1 General Description

This is a single arm, open label, exploratory study to evaluate the efficacy of Valchlor in the treatment of LPP. Subjects will be screened by the Department of Dermatology at the Mayo Clinic in Florida outpatient clinic and interested qualified subjects will be consented and offered participation. This study is designed to establish feasibility and proof of concept and will not include randomization or crossover components.

Patients with biopsy proven LPP who have failed one prior topical or systemic therapy with evidence of active disease will be eligible to participate. The presence of active disease will be based on a baseline clinical exam showing perifollicular erythema with scaling. Patients with predominance of end stage scarring hair loss but without significant active erythema will be excluded. Involvement restricted to the frontal scalp is a recognized clinical variant of LPP and is known as frontal fibrosing alopecia (FAA). As the histological features of LPP and FAA are identical, patients with FAA subtype of LPP would also be eligible to participate in the study.

Eligible participants using high-potency topical corticosteroids, intralesional corticosteroids, or oral hydroxychloroquine may enroll but will be required to discontinue use during the study period.

All study participants will apply Valchlor 0.016% gel to involved areas at night, beginning with three times a week (Mondays, Wednesdays and Fridays) and increasing to daily application after one month, if well tolerated. Patients will be instructed to first part the hair away from involved area as needed, limit application to areas with alopecia and erythema, apply 30 minutes after showering or washing, and allow treated areas to dry for 5 to 10 minutes before covering with clothing or going to bed. Participants will be instructed to wash their hands with soap and water after applying Valchlor. Caregivers who assist in application will be instruction to wear disposable nitrile gloves when applying Valchlor and dispose with the household trash. Patients will be instructed to store Valchlor in the refrigerator away from foods at 36°F - 46°F and apply within 30 minutes after removing from refrigeration.

3.2 Number of Subjects

Twenty

3.3 Duration of Participation

Six months

3.4 Primary Study Endpoints

The primary outcome measure of efficacy will be the percent reduction of baseline Lichen Planopilaris Activity Index (LLPAI) score after 6 months of treatment defined as follows.

- Complete response: LLPAI reduction greater than 85% from baseline score.
- Partial response: LLPAI reduction of between 25-85% from baseline score.
- Non-response: LLPAI reduction of less than 25% from baseline score.

The Lichen Planopilaris Activity Index (LPPAI) is a standardized validated quantitative measure of disease activity [12]. LPPAI score (0-10) is calculated as follows: (pruritus + pain + burning)/3 + (scalp erythema + perifollicular erythema + perifollicular scale)/3 + 2.5 (pull test) + 1.5 (spreading/2). Symptoms and signs are graded on a 4-point scale with 0 = absent, 1 = mild, 2 = moderate, and 3 =severe. Clinical progression and a positive hair pull test are graded 1=yes; 0=no.

3.5 Secondary Study Endpoints

The secondary outcome measures of efficacy at baseline and after 6 months of treatment will include:

- Mean follicular density as assessed using Canfield scalp photography
- Dermatology Quality of Life Index (DQLI) score : 10 standardized items measuring impact of skin disease rated as 0=not at all/not relevant; 1=a little; 2=a lot; 3=very much
- Physician Global Assessment (PGA) score : using standardized photography compared to the presenting baseline and scored as -1 = worse (no change to erythema with new areas of alopecia); 0 = no change; 1 = mild improvement (slight reduction in erythema, alopecia not progressive); 2= moderate (moderate reduction in erythema, alopecia not progressive); 3 = significant improvement (very mild erythema, alopecia not progressive); 4 = clear (no erythema, alopecia not progressive)

3.6 Primary Safety Endpoints

The primary safety endpoint of this study will be the number of days between unintentional mucosal and/or ocular exposure during the study period.

3.7 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- Baseline and interval changes to medical history
- LLPAI score
- DQLI score
- PGA score
- Screening and documentation of Adverse Events
- Phototrichograms for hair count using Fotofinder video-epiluminescence microscopy in combination with the Trichoscan digital image analysis

The following source data will not be directly recorded in the CRF, but will be captured in supportive documentation to include study source documents and the EMR:

- Laboratory results and clinical interpretation of the values
- Standardized clinical photography

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

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

- Male and female patients 18 years or older.
- Biopsy proven diagnosis of Lichen Planopilaris
- Biopsy proven diagnosis of Fontal Fibrosing Alopecia (a clinical variant of LPP restricted to frontal scalp)
- Good general health as confirmed by medical history
- 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
- Pregnant or nursing women
- Women planning a pregnancy within the study period
- Active smokers
- Known history of adverse reaction to mechlorethamine
- Use of systemic immunosuppressive
- Presence of ulcerated scalp lesions

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited from the Department of Dermatology at the Mayo Clinic in Florida outpatient clinical practice. All referring dermatologic physicians to Mayo Clinic Florida in the Southeastern United States will also be mailed a notice advising of the availability of this study. Patients may be directly referred for participation by these providers with all screening and follow-up exams performed at Mayo Clinic in Florida. 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 may be replaced within the accrual period. 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 and/or Investigators' judgment, the patient's condition required another form of treatment
- Mechlorethamine sensitization: Patient develops contract dermatitis to Valchlor that cannot be managed with low potency topical corticosteroids
- Inclusion/Exclusion Discrepancy/Violation: Patient should not have been enrolled
- 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

VALCHLOR is a topical product that contains mechlorethamine HCl, an alkylating drug. Mechlorethamine HCl is a white to off white solid that is very soluble in water and methanol, partially soluble in acetone, and generally not soluble in organic solvents.

Mechlorethamine HCl is designated chemically as 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride. The molecular weight is 192.52 and the melting point is 108-111°C. The empirical formula is C5H11Cl2N•HCl, and the structural formula is: CH3N(CH2CH2Cl)2•HCl.

Each tube of VALCHLOR contains 60g of a gel containing 0.016% w/w of mechlorethamine (equivalent to 0.02% mechlorethamine HCl) in a base of the following inactive ingredients: diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerin, lactic acid, hydroxypropylcellulose, sodium chloride, menthol, edetate disodium, butylated hydroxytoluene.

Systemic exposure was undetectable after topical administration of VALCHLOR to patients. Blood samples were analyzed from 16 and 15 patients following treatment with VALCHLOR (mechlorethamine gel 0.016%) and an identical formulation consisting of mechlorethamine 0.032% w/w, respectively. For patients who received mechlorethamine 0.016%, samples were collected to measure mechlorethamine concentrations prior to dosing, on day 1, and at the first month visit. Following the topical administration of mechlorethamine 0.016%, there were no detectable plasma mechlorethamine concentrations observed in any of the patients. Patients who received mechlorethamine 0.032% had no measurable concentrations of mechlorethamine or half-mustard after 2, 4, or 6 months of treatment.

5.2 Treatment Regimen

All study participants will apply Valchlor 0.016% gel to involved areas at night, beginning with three times a week, (Mondays, Wednesdays and Fridays) and increasing to daily application after one month, if well tolerated, for a total of 6 months. Patients will be instructed to first part the hair away from involved area as needed, limit application to areas with alopecia and erythema, apply 30 minutes after showering or washing, and allow treated areas to dry for 5 to 10 minutes before covering with clothing or going to bed. Participants will be instructed to wash their hands with soap and water after applying Valchlor. Caregivers who assist in application will be instruction to wear disposable nitrile gloves when applying Valchlor and dispose with the household trash. Patients will be instructed to store Valchlor in the refrigerator away from foods at 36-46 degrees F and apply within 30 minutes after removing from refrigeration.

5.3 Method for Assigning Subjects to Treatment Groups

This is an open-label pilot investigation and all study participants are assigned to active treatment with a topically applied study drug. There is no placebo arm in this study.

5.4 Preparation and Administration of Study Drug

The study drug will be stored and dispensed to patients at each study visit from the Mayo Clinic Florida Research Pharmacy.

5.5 Subject Compliance Monitoring

Study participants will be dispensed one 60 gram tube at the qualifying baseline exam, 2 tubes at week 4 following phone visit, and 3 tubes at the week 12 follow-up visit. They will be instructed to use one tube per 30 days and be will instructed to bring these tubes for all follow-up visits. Weights of each tube after 30 days of use will be recorded.

5.6 Prior and Concomitant Therapy

Eligible participants using high-potency topical corticosteroids, intralesional corticosteroids, or oral hydroxychloroquine may enroll but will be required to discontinue use during the 6 month study duration.

Mild irritant reactions at site application may be treated with class IV topical corticosteroids in a gel vehicle the morning following nightly application on an as needed basis.

5.7 Packaging

Each tube of VALCHLOR contains 60g of a gel containing 0.016% w/w of mechlorethamine (equivalent to 0.02% mechlorethamine HCl) in a base of the following inactive ingredients: diethylene glycol monoethyl ether, propylene glycol, isopropyl alcohol, glycerin, lactic acid, hydroxypropylcellulose, sodium chloride, menthol, edetate disodium, butylated hydroxytoluene.

Study drug will be shipped to the Mayo Clinic research pharmacy in Florida and labeled upon receipt with statement "Caution: New Drug Limited by Federal law for investigational use."

5.8 Masking/Blinding of Study

This is an open-label pilot investigation. Masking and blinding procedures are not applicable. Qualitative and quantitative evaluations of response to treatment will be recorded. Updated photographs will be included in participants' records at each visit.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The drug will be shipped by Actelion Pharmaceuticals US, Inc to the Mayo Clinic research pharmacy in Florida. Upon receipt of the of the study drug, an inventory will be performed and a drug receipt log filled out by the person accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted in the shipping invoice. Any discrepancies, damaged or unusable study drug in a given shipment will be documented in the study files. The sponsor-investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

5.9.2 Storage

Prior to dispensing, Valchlor will be stored in the freezer at -13°F to 5°F (-25°C to -15°C). After dispensing, patients will be advised to store Valchlor in a refrigerator at 36°F - 46°F (2°C - 8°C). Patients should consult a pharmacist prior to using Valchlor that has been left at room temperature for longer than one hour per day.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team. Drug dispensation will occur at scheduled follow-up visits.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Remaining drug will be destroyed on site will be documented in the study files. Participants will be required to return any unused study drug at the end of the study period.

6 Study Procedures

6.1 Visit 1 (Week 0/Baseline)

a) Informed consent
b) Review treatment protocol
c) LPPAI baseline score
d) PGA baseline score
e) DLQI baseline score
f) Review medical history and current medications
g) Baseline photographs
h) Assessments of hair density using phototrichograms
i) Dispense 1 tube of study drug
j) Urine Pregnancy Test (female patients of childbearing potential); start/confirm form of contraception

6.2 Visit 2 (Week 4 Phone Follow-up)

a) Phone follow-up visit to assess any adverse reactions (if any)
b) Dispense 2 tubes of study drug

6.2 Visit 3 (Week 12± 5 days)

a) LPPAI score
b) Review changes to medical history and current medications
c) Screen/Review adverse events
d) Repeat photographs
e) Assessments of hair density using phototrichograms
f) Dispense 3 tubes and reconcile study drug
g) Review compliance
h) Urine Pregnancy Test (female patients of childbearing potential); confirm form of contraception

6.3 Visit 4 (Week 24± 5 days)

a) LPPAI score final
b) PGA score final
c) DLQI score final
d) Review changes to medical history and current medications
e) Screen/review adverse events
f) Repeat photographs
g) Assessments of hair density using phototrichograms
h) Reconcile and collection of unused study drug
i) Urine Pregnancy Test (female patients of childbearing potential); confirm form of contraception

	Schedule of Events			
Study Activity	**Day 1 SCREENING BASELINE**	**Week 4 PHONE FOLLOW-UP**	**Week 12 FOLLOWUP**	**Week 24 FOLLOWUP**
Visit Number	**1**	**2**	**3**	**4**
Allowable visit window in days		**+/- 5**	**+/- 5**	**+/- 5**
Review Eligibility	X			
Informed Consent	X			
Medical History	X			
Dispense/Reconcile Medications	X	X	X	X
Review Changes to Med History and Medications			X	X
LPPAI	X		X	X
PGA	X			X
DLQI	X			X
B-HCG (females)	X		X	X
Photographs/Hair Count	X		X	X
Review Valchlor Application Instructions	X		X	X
Screening for Adverse Events		X	X	X

7 Statistical Plan

7.1 Sample Size Determination

Due to the pilot nature of the study, no formal statistical power or sample size calculations are necessary. The sample size of 20 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

Descriptive Statistics

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

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.

Primary Hypothesis:

The primary endpoint for this study is the LPPAI score. While a minimal clinically significant difference for this outcome measure has not been established, clinically meaningful treatment responses will generate large changes in the LPPAI score given the weightings used in the underlying formula. Therefore, the proposed minimal accrual target of twenty patients will be adequate for the preliminary data generating purposes of an exploratory study. A larger sample size to detect smaller changes in the LPPAI score is not needed as small differences in the LPPAI score are not clinically meaningful. The minimal accrual target of 10 is achievable given an estimated incidence of LPP/FAA of 1-3% in tertiary hair loss centers. The definitions of complete response, partial response, and non-response will be defined using standardized LLPAI scoring which will permit a relative comparison of treatment efficacy to previously published systemic treatments using hydroxychloroquine and mycophenolate mofetil.

Interim Analysis

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

7.3 Subject Population(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 results 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 local investigator 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 Investigator's Brochure, 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 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 investigator 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. .

Initial screening for AE will include non-directed questioning of the patient at each follow-up visit during the study period along with the directed questioning and examination regarding:

- Signs and symptoms of idiosyncratic allergic contact dermatitis

Patients will be instructed to stop using Valchlor and to contact the study coordinator if swelling and blistering occurs as this may represent early signs of allergic contact dermatitis. The primary investigator will then evaluate the patient and if the signs and symptoms are

compatible with allergic contract dermatitis, the patient will be offered treatment using a medium-potency topical corticosteroid to involved areas in the AM, with resumption of Valchlor application in the PM. Patients with persistent allergic contact dermatitis reactions unable to be managed as outlined above will exit the study.

- Unintentional mucosal and/ocular exposure

Patients will be warned not to apply Valchlor near eyes, mouth, or nose as it can cause pain, redness, swelling, burning, sensitivity to light, blurred vision, and blindness or permanent eye injury. If accidental Valchlor exposure to nose, mouth or eyes occurs, patients will be instructed to rinse affected areas with large amounts of water for 15 minutes and to contact the study coordinator. The primary investigator will then contact the patient to review application site instructions and schedule a follow-up evaluation if the patient reports persistent symptoms or erythema.

Serious Adverse Event
Adverse events defined as serious will the following:

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly
- medically significant

Medically Significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

All adverse events that do not meet any of the criteria for serious, will be regarded as **non-serious adverse 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 will 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 will also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-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-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
Any clinical laboratory abnormality that can reasonably be related to the topical administration of Valchlor 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 topical use of Valchlor.

8.2 Recording of Adverse Events

At each contact with the subject, the study team will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly clinically related signs, symptoms, and abnormal diagnostic, laboratory or procedure results will be recorded in the source document.

All adverse events occurring during the study period will 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 during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported to Actelion immediately (see 8.3 below).

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required. All SAEs considered possibly as related to study medication by the Sponsor-Investigator must be reported immediately to Actelion Global Drug Safety (GDS) as set forth in the IIS agreement (on Actelion SAE template FRM-001093). Actelion reserves the right to request additional information and clarifications on cases forwarded by the Sponsor-Investigator.

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

8.3.1 Sponsor-Investigator reporting: notifying the Mayo 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, FDA and Actelion. 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 Sponsor-Investigator reporting: Notifying the Actelion

This protocol is not being conducted under an FDA investigational new drug application.

Any AE reports meeting reporting criteria obligation (serious and possibly related to Valchlor) need to be reported to Actelion immediately.

Actelion Global Drug Safety will report any safety information received from SPONSOR-INVESTIGATOR to the competent Health Authorities as per regulatory reporting requirements regarding marketed products.

Additionally, if any AE or actions taken for safety reasons are sent directly to FDA by SPONSOR-INVESTIGATOR, copy of the same notification must also be sent in copy immediately to Actelion with clear notation regarding FDA notification.

8.4 Unmasking/Unblinding Procedures

This is an open-label pilot investigation. Unmasking and 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 high incidence of contact dermatitis that cannot be managed with low potency topical steroids.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). 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 (HIPAA). 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, microfiches, 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.

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. All entries will be printed

legibly in black ink. 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

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 Processing

All study date will be stored and analyzed at Mayo Clinic in Florida.

Data Security and Confidentiality

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

Data Quality Assurance

Once the study is completed the Principal Investigator will randomly select 3 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 20 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 sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and

delivery of the drug for investigational use is discontinued and Actelion has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" and as outlined in the Actelion Investigator Initiated Study Agreement.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator 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 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 sponsor-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 must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent. This study will not include vulnerable study populations.

12 Study Finances

12.1 Funding Source

This investigator initiated study is funded by Actelion Pharmaceuticals.

12.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

No financial conflicts of interested are anticipated for this study.

12.3 Subject Stipends or Payments

No payment is given to study participants.

13 Publication Plan

The primary responsibility for publication of the study results is with the Primary Investigator. After the complication of study and prior to publication, the study results will be shared with Actelion Pharmaceuticals. The study will be registered at ClinicalTrials.gov prior to subject recruitment along with the posting of the results within 12 months of final data collection for the primary outcome measure.

14 References

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15 Attachments

None