Mycosis fungoides cutaneous T-cell lymphoma

Protocol AC-079A501

PROVe

A PROspective, observational, US-based study assessing outcomes, adverse events, treatment patterns, and quality of life in patients diagnosed with mycosis fungoides cutaneous T-cell lymphoma and treated with Valchlor®

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Document type:	Protocol for Non-Drug Interventional and Non-interventional (Observational) Studies using Epidemiological Methods
Document status and version:	Final Version 3
Date:	13 December 2016
Number of pages:	43
Document number:	D-16.626

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Hereinafter called Actelion

TITLE: A prospective, observational, US-based study assessing outcomes, adverse events, treatment patterns, and quality of life in patients diagnosed with mycosis fungoides cutaneous T-cell lymphoma and treated with Valchlor®

PROTOCOL NUMBER: AC-079A501

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Disease area

Mycosis fungoides cutaneous T-cell lymphoma

Protocol number, acronym, study title, version

Protocol AC-079A501, PROVe, A prospective, observational, US-based study assessing outcomes, treatment patterns, adverse events, and quality of life in patients diagnosed with mycosis fungoides cutaneous T-cell lymphoma and treated with Valchlor®. Final Version 3.

I agree to the terms and conditions relating to this study as defined in this protocol and any other protocol-related documents.

NAME (TITLE)	CITY	STATE	DATE	SIGNATURE

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
BSA	Body surface area
CAILS	Composite Assessment of Index Lesion Severity
CTCL	Cutaneous T-cell lymphoma
DCF	Data clarification form
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data collection
EOS	End of study
FDA	Food and Drug Administration
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MCH	Mechlorethamine hydrochloride
MCN	Manufacturer's Control Number
MedDRA	Medical Dictionary for Regulatory Activities
MF-CTCL	Mycosis fungoides cutaneous T-cell lymphoma
MF/SS-CTCL	Mycosis fungoides / Sézary syndrome-type cutaneous T-cell lymphoma
mSWAT	Modified Severity Weighted Assessment Tool
QOL	Quality of life
SAE	Serious adverse event
TNMB	Tumor-node-metastasis-blood
VAS	Visual Analogue Scale

PROTOCOL SYNOPSIS AC-079A501

This abstract is a stand-alone summary of the study protocol

TITLE	A **PRO**spective, observational, US-based study assessing outcomes, adverse events, treatment patterns, and quality of life in patients diagnosed with mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) and treated with **V**alchlor®
ACRONYM	PROVe
AUTHOR	Badri Rengarajan, Actelion Pharmaceuticals US, Inc.
RATIONALE AND BACKGROUND	Due to the rarity of mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL), there is a dearth of epidemiologic data detailing the clinical course of the disease and its response to treatment. While topical treatment with mechlorethamine hydrochloride (MCH) has been used since the 1950s, prospective data describing the clinical course of MF-CTCL is limited. Valchlor gel is a new formulation of MCH (or nitrogen mustard) that has been shown to be safe and effective in a clinical trial and has been approved for Stage I MF-CTCL patients Prospective data on Valchlor are currently only available from the pivotal, randomized, controlled clinical trial with strict inclusion and exclusion criteria. Understanding real-world patient safety and tolerability, as well as compliance and discontinuation rates, will assist with the management of Valchlor-treated MF-CTCL patients. This study will build and extend on the data from the Valchlor clinical development program, increase the understanding of the use of Valchlor in patients with MF-CTCL and, while limited to patients treated with Valchlor, will represent the largest prospective study with any given MF-CTCL treatment. This large, non-interventional study will provide information on the use of Valchlor in a 'real-world' clinical practice setting, and increase understanding of the management and outcomes of Valchlor-treated MF-CTCL patients. Data collected includes, but is not limited to: outcomes (e.g., clinical status and healthcare utilization [MF-CTCL-related hospitalizations and emergency room visits]), adverse events (AEs; e.g., dermatitis), clinical characteristics, and treatment patterns. Finally, this study will document disease burden (e.g., pruritus) of MF-CTCL in a real-life

	setting by collecting patient-completed symptoms and quality of life (QOL) questionnaires for patients with skin disease. The QOL tools include VAS, Skindex-29 and a newly validated Mycosis fungoides / Sézary syndrome-type cutaneous T-cell lymphoma (MF/SS-CTCL) questionnaires.
RESEARCH QUESTION AND OBJECTIVES	The objectives of this study are: • To describe clinical characteristics of patients treated with Valchlor at enrollment and during the study observation period. • To describe treatment and response assessment patterns of patients with MF-CTCL treated with Valchlor at enrollment and during the study observation period. • To assess outcomes (e.g., clinical status and rates of healthcare utilization [MF-CTCL-related hospitalizations and emergency room visits]) in patients with MF-CTCL treated with Valchlor during the study observation period. • To collect and describe the incidence of AEs/serious adverse events (SAEs) in patients with MF-CTCL treated with Valchlor: o To estimate the incidence of dermatitis in patients using Valchlor during the study observation period. o To describe the management of dermatitis in patients using Valchlor at enrollment and during the study observation period. • To collect patient-completed symptoms and QOL questionnaires.
STUDY DESIGN	This is a multi-center, prospective, observational, US-based drug study. All consecutive MF-CTCL patients being treated with Valchlor will be invited to enroll in this study. Patients will undergo clinical assessments and receive standard medical care, as determined by the patients' physician, in the real-world setting. With the exception of protocol-required patient-completed questionnaires for symptoms and QOL, there are no specific or mandated clinical assessments to be performed, and patients will not receive experimental intervention or treatment as a consequence of their participation in this study. Patients will be followed prospectively for a maximum of 2 years

	from the date of signed informed consent (enrollment) until end of study, which includes withdrawal of consent, loss to follow-up, death, or study completion. Continuation in the study is not contingent on continuation of Valchlor. Patients currently enrolled and ongoing or newly enrolled will be offered to participate in the 24-month study of this protocol Amendment 1. Patients who enrolled under the original protocol (prior to Amendment 1) and are still ongoing in the study will be re-consented and to follow data collection specified in Table 1 of this protocol for a total of 24 months from original consent date. Patients who enrolled and have completed 1 year of the study under the original protocol will not be re-consented under Amendment 1.
POPULATION (SETTING AND STUDY POPULATION)	This study will enroll approximately 300 consecutive patients diagnosed with MF-CTCL and being treated with Valchlor, regardless of other MF-CTCL therapies received before or at enrollment. Patients will be enrolled from up to 50 participating centers/clinics in university-affiliated or community hospitals in the US. The participation of physicians and patients in the study is on a voluntary basis. Inclusion criteria: • All adult patients (≥ 18 years of age) diagnosed with MF-CTCL and being treated with Valchlor. This includes patients newly initiating Valchlor OR patients continuing treatment with Valchlor: o Patients newly initiating Valchlor are patients who have their first office visit after having initiated Valchlor. o Patients continuing treatment with Valchlor includes patients who are actively taking Valchlor on the day of enrollment. o Signed patient informed consent. Exclusion criteria: • None
VARIABLES	The variables of interest for this study includes clinical characteristics, treatment patterns, clinical status, as assessed by the physician (including the methods used in practice to assess clinical status), MF-CTCL-related healthcare utilization, as assessed by the physician (hospitalizations and emergency room visits), AEs and

	SAEs, patient-completed symptoms and QOL questionnaires. Due to expected variability in practice patterns, no individual method of determining response is mandated, but assessments that do occur must be captured prospectively. Additionally, it is important to capture which methods were used pre-study, even where results may not be available, so that it is clear which assessments have a prior assessment that may have been considered in the physician's evaluation of response. The specific outcomes and variables of interest for the study are: Clinical characteristics. Relevant medical history, including tumor-node-metastasis-blood (TNMB) classification. Use of prior MF-CTCL treatments. Treatment patterns, including prescribing information, for the treatment of MF-CTCL (including dosing regimens, titration schemes, duration of time from initiation to discontinuation of therapy, and drug holidays for Valchlor). Clinical status, as assessed by the physician (i.e., complete response, partial response, stable disease, progressive disease, relapse). Assessments (both whether or not the assessment was performed and the result of the assessment) used to define response, including, but not limited to: o Composite Assessment of Index Lesion Severity (CAILS). o Modified Severity Weighted Assessment Tool (mSWAT). o Physician's Global Assessment. o Body Surface Area (BSA) of disease. Healthcare utilization related to MF-CTCL during the study period, as assessed by physician: o Number of MF-CTCL-related hospitalizations. o Number of MF-CTCL-related emergency room visits. AEs and SAEs (e.g., dermatitis) whether or not related to Valchlor.

	Patient-completed questionnaires: o Visual Analogue Scale (VAS) for pruritus (scale 0–10). o Skindex-29. o MF/SS CTCL.
DATA SOURCES	Information will be collected per routine clinical practice. No specific clinical mandated assessments are to be performed as part of study participation. Patient-completed questionnaires, however, are a study requirement and will be collected at all clinic visits during the study observation period. These questionnaires will be administered on paper by study coordinators. Patient clinical data (non-patient-completed) will be collected from the patient's medical records at enrollment and throughout the study period. All data will be entered into electronic Case Report Forms (eCRFs) at the time of collection or on a quarterly basis by study coordinators. AEs and SAEs whether or not related to Valchlor will be entered into the eCRF at every visit and upon notification by the patient (e.g., reported via phone call). For patients who do not have any visits, an affirmative response that the patient is still under care by the site will be requested quarterly, so that the absence of reported assessments can be interpreted the same as the actual absence of actual assessments. **Pre-treatment** information will be collected **at the time of enrollment** using the following variables: • Weight • TNMB classification • Use of Valchlor and other MF-CTCL treatments • Assessments used to define response (whether or not the assessment was ever performed, and regardless of whether the assessment was used to assess response for a previously treated patient or whether the assessment was performed for a comparison with future evaluations of response, and the results of the most recent assessments), including, but not limited to: o CAILS. o mSWAT. o Physician's Global Assessment. o BSA of disease. In addition, the following information will be collected **at the time**

	of enrollment: Patient demographics. Relevant medical history MF-CTCL TNMB classification. MF-CTCL histology. Use of Valchlor and other MF-CTCL treatments (including start and stop dates for each medication, and reasons for starting and stopping medications). Clinical status, as assessed by the physician (i.e., complete response, partial response, stable disease, progressive disease, relapse). Assessments (both whether or not the assessment was performed and the result of the assessment) used to assess response, including, but not limited to: o CAILS. o mSWAT. o Physician's Global Assessment. o BSA of disease. All ongoing AEs and SAEs. Patient-completed questionnaires: o VAS for pruritus (scale 0–10). o Skindex-29. o MF/SS CTCL The following information will be collected at all clinic visits occurring **during the observation period**: MF-CTCL TNMB classification changes. Changes in relevant medical history. Use of Valchlor and other MF-CTCL treatments (including start and stop dates for each medication, and reasons for starting and stopping medications). Healthcare utilization related to MF-CTCL since the last study visit, as assessed by physician: o Number of MF-CTCL-related hospitalizations

	(including length of stay and primary admission and discharge diagnoses). o Number of MF-CTCL-related emergency room visits. Clinical status, as assessed by physician (i.e., complete response, partial response, stable disease, progressive disease, relapse). Assessments (whether or not the assessment was performed and the result of the assessment) used to assess response, including, but not limited to: o CAILS. o mSWAT. o Physician's Global Assessment. o BSA of disease. All AEs and SAEs (e.g., dermatitis) whether or not related to Valchlor, including reports of secondary exposures since last visit (while on Valchlor only). Patient-completed questionnaires: o VAS for pruritus (scale 0–10). o Skindex-29. o MF/SS-CTCL. Patients who enrolled under the original protocol and are still ongoing in the study will be contacted and informed consent will be obtained for the Amendment 1 protocol. Patients prospective data will be collected up to a total of 24 months from the original enrollment date.
STUDY SIZE	This study will enroll approximately 300 patients diagnosed with MF-CTCL who are being treated with Valchlor. A sample size of 270 evaluable patients is needed to estimate the percentage of patients with clinical status and the rate of hospitalizations, both with a margin of error of 6 percentage points. Assuming that up to 10% of patients may be non-evaluable due to incomplete follow-up, the sample size target for enrollment should be 300. It is projected that approximately 200 evaluable patients currently enrolled will be re-consented and newly enrolled will be consented under Amendment 1 for a 2-year follow-up. The margin of error for 200 evaluable patients will be 7%. Additionally, it is important to be able to estimate these same

	percentages with a margin of error of 10 percentage points or less for key subgroups representing a third or more of the patient population (e.g., patients newly initiating Valchlor). A total of 100 patients are required to achieve a margin of error of 10 percentage points, so that a total enrollment of 300 patients is needed.
DATA ANALYSIS	Demographics and clinical characteristics will be summarized for all patients enrolled as well as grouped separately for patients continuing treatment with Valchlor versus patients who are newly initiating Valchlor. Use of prior treatments and past methods of assessing response will similarly be analyzed separately for the two groups. Treatments individually and in combination will be reported in percentage terms, by visit, stratified by newly initiating patients and continuing patients to identify treatment patterns. Analyses of response, based on a particular measure of response, will be limited to patients for whom that measure was reported. Therefore, patients with reported data will be summarized also for patients without any reported data with respect to demographics and pre-treatment clinical status to identify potential biases. Rates of on-study hospitalization and emergency room visits will be computed as the utilization counts divided by on-study days. The summary of response rates will be tabulated and the definition of response will be detailed in the Statistical Analysis Plan. The frequency and percentage of patients experiencing any AEs or SAEs will be summarized by system organ class and preferred MedDRA terminology. SAEs requiring hospitalizations and fatal SAEs will be displayed in patient listings. At each visit performed during the observation period (1st, 2nd, etc.), the VAS for pruritus, the three scales of the Skindex-29 and the MF/SS-CTCL questionnaires will be computed for patients who are and are not responders. These descriptive cross-sectional comparisons are intended to assess burden of disease in a Valchlor-treated cohort over time.
MILESTONES	First patient, first visit: Q4 2014 Last patient, first visit: Q3 2017 Last patient, last visit: Q3 2019

DATA OWNERSHIP	Actelion Pharmaceuticals US, Inc.
STUDY COMMITTEE(S)	The Scientific Committee will consist of 4–6 key opinion leaders in the field of MF-CTCL who will provide scientific input on the MF-CTCL Study protocol and review study data.

PROTOCOL

1 AMENDMENTS AND UPDATES (PROTOCOL HISTORY)

The protocol version 2, dated 12 November 2014, Appendix A, Appendix B and section 5.7.6 for the Skindex-29 Questionnaire were updated. As these were administrative changes, no amendment was required; only a new protocol version number was issued. The protocol Amendment 1 will originate version 3 to extend ongoing patients and newly enrolled patients for a total of 24 months from consent date. An additional new quality of life assessment has been added.

2 STUDY MILESTONES

This study will be conducted according to the following schedule:

First patient, first visit: Q4 2014

Last patient, first visit: Q3 2017

Last patient, last visit: Q3 2019

3 RATIONALE AND BACKGROUND

Background

Mycosis fungoides cutaneous T-cell lymphoma (MF-CTCL) can present as patches, plaques, or tumors on the skin, often in areas of the body that are not usually exposed to the sun [Lymphoma.org 2011]. While MF-CTCL is rare, it is the most common type of cutaneous T-cell lymphoma (CTCL), accounting for 50–70% of all CTCLs [Imam 2013]. It is estimated that approximately 16,000 to 20,000 people in the US have the disease and that the 5-year incidence of MF-CTCL for all stages was 0.56 per 100,000 person-years between 2005–2009 [Korgavkar 2013, Leukemia & Lymphoma Society 2011]. The prevalence and incidence of MF-CTCL are likely to be under-reported due to nomenclature variances and because the symptoms and skin biopsy findings can appear similar to other types of skin conditions [Lymphoma.org 2011, Criscione 2007]. Patients frequently present with early stage disease typically associated with a favorable prognosis and survival of 10–35 years, but over 25% progress to advanced disease with a median survival of less than 4 years and just 13 months in those with nodal involvement [Scarisbrick 2014]. The most important clinical predictive factors for survival include patient age, T classification, and the presence of extracutaneous disease [Kim 2003a].

Although there is currently no cure for the disease, patients diagnosed at early stages of MF-CTCL (Stages IA, IB, or IIA) and receiving treatment for the disease have a median survival of 35.5, 21.5, and 15.8 years, respectively [Agar 2010]. Topical mechlorethamine hydrochloride (MCH or nitrogen mustard) has been used to treat

MF-CTCL since the 1950s [Lessin 2013]. The National Comprehensive Cancer Network [NCCN] Guidelines list topical MCH as a primary skin-directed treatment option for patients with MF-CTCL with limited/localized skin involvement or for generalized skin involvement [NCCN 2014]. Topical MCH has been available in aqueous and petrolatum-based forms. However, both forms have disadvantages that limit patient acceptance [Kim 2003b, Ramsay 1995].

Valchlor, approved by the FDA in August 2013 for Stage IA and IB MF-CTCL, is a fast-drying, greaseless gel formulation that has been shown to be effective and safe in a clinical trial [Lessin 2013]. Two hundred sixty (260) patients in the Valchlor clinical trial (Study 201) received MF-CTCL specific treatment up to 12 months [Lessin 2013]. In the open-label, single group extension trial, 98 patients who completed Study 201 without a complete response received treatment with a formulation identical to Valchlor but containing MCH HCl 0.04% for 7 months. Currently, Valchlor is the only FDA-approved formulation of topical MCH, and one of two FDA-approved topical treatments for MF-CTCL [Kim 2014]. The results of the randomized, controlled, multi-center trial confirmed the non-inferiority of Valchlor in the treatment of MF-CTCL when compared to ointment-based MCH.

Rationale

Prospective data on Valchlor are currently only available from the pivotal, randomized, controlled clinical trial with strict inclusion and exclusion criteria. Understanding real-world patient safety and tolerability, as well as compliance and discontinuation rates, will assist with the future management of Valchlor-treated MF-CTCL patients. This study will build and extend on the data from the Valchlor clinical development program, increase the understanding of the use of Valchlor in patients with MF-CTCL and, while limited to patients treated with Valchlor, will represent the largest prospective study with any given MF-CTCL treatment.

This large, non-interventional study will provide information on the use of Valchlor in a 'real-world' clinical practice setting. This study will increase understanding of the management and outcomes of Valchlor-treated MF-CTCL patients by observing clinical characteristics, treatment patterns, outcomes (e.g., clinical status and healthcare utilization [MF-CTCL-related hospitalizations and emergency room visits]), and adverse events (AEs). Additionally, a better understanding of the disease burden of MF-CTCL will be gained by collecting patient-completed symptoms and quality of life (QOL) questionnaires.

4 RESEARCH QUESTION AND OBJECTIVES

The objectives of the MF-CTCL prospective cohort study are:

- To describe clinical characteristics of patients treated with Valchlor at enrollment and during the study observation period.
- To describe treatment and response assessment patterns of patients with MF-CTCL treated with Valchlor at enrollment and during the study observation period.
- To assess outcomes (e.g., clinical status and rates of healthcare utilization [MF-CTCL-related hospitalizations and emergency room visits]) in patients with MF-CTCL treated with Valchlor during the study observation period.
- To collect and describe the incidence of AEs/SAEs in patients with MF-CTCL treated with Valchlor:
    - To estimate the incidence of dermatitis in patients using Valchlor during the study observation period.
    - To describe the management of dermatitis in patients using Valchlor at enrollment and during the study observation period.
- To collect patient-completed symptoms and QOL questionnaires.

5 RESEARCH METHODS

5.1 Study design

This is a multi-center, prospective, observational study of MF-CTCL patients who have newly initiated Valchlor or who are continuing treatment with Valchlor.

Patients will be followed by their physician according to routine clinical practice. With the exception of protocol-required patient-completed questionnaires, there are no specific or mandated clinical assessments to be performed, and patients will not receive experimental intervention or treatment as a consequence of their participation in this study. The study protocol will not mandate any specific schedule of visits. Patients will undergo clinical assessments and receive standard medical care as determined by the patient's physician in a real-world setting.

Patients will be followed prospectively for a maximum of 2 years from the date of signed informed consent until end of study (EOS), which includes withdrawal of consent, loss to follow-up, death, or study completion. Continuation in the study is not contingent on continuation of Valchlor.

The study will end after all enrolled patients have been followed for 2 years, or discontinued from the study for any reason.

5.2 Population (setting and study population)

This study will enroll approximately 300 MF-CTCL patients being treated (newly initiated or continuing treatment) with Valchlor [see Section 5.2.1 for details] from up to 50 participating centers/clinics in university-affiliated or community hospitals.

Patients considered 'being treated with Valchlor' is comprised of two distinct groups: 1) Patients newly initiating Valchlor. These are patients who are enrolled at their first office visit after having initiated Valchlor; 2) Patients continuing treatment with Valchlor. Patients must be actively taking Valchlor on the day of enrollment.

All consecutive MF-CTCL patients being treated with Valchlor [see Section 5.2.1 for details] seen at the participating centers are eligible for enrollment in the study, regardless of other MF-CTCL therapies received before or at the time of enrollment.

5.2.1 Inclusion criteria

- All adult patients (≥ 18 years of age) diagnosed with MF-CTCL and being treated with Valchlor. This includes patients newly initiating Valchlor OR patients continuing treatment with Valchlor:
    - Patients newly initiating Valchlor are patients who have their first office visit after having initiated Valchlor.
    - Patients continuing treatment with Valchlor includes patients who are actively taking Valchlor on the day of enrollment.
- Signed patient informed consent.

5.2.2 Exclusion criteria

- None.

5.3 Variables

The variables of interest for this study includes clinical characteristics at enrollment and during the study observation period, treatment patterns, clinical status, as assessed by the physician (including the methods used in practice to assess clinical status), MF-CTCL-related healthcare utilization, as assessed by the physician (hospitalizations and emergency room visits), AEs and SAEs, patient-completed symptoms and QOL questionnaires.

Data elements to be collected from the patient's medical record at study enrollment and at post-enrollment follow-up visits are shown in Table 1. Additionally, pre-treatment data collection using specific variables will be performed at enrollment. These variables include weight, tumor-node-metastasis-blood (TNMB) classification, use of Valchlor and other MF-CTCL treatments, and clinical status assessments. Drug holidays (temporary discontinuation) from Valchlor will be captured on the electronic Case Report Form (eCRF) by recording start and stop dates of all MF-CTCL treatments. Patient-completed questionnaires will be administered to patients who can read and understand English or Spanish and are able to self-complete the questionnaires based on the investigator's assessment. Patients who are unable to read and understand English or Spanish will not be asked to complete the questionnaires and will be excluded from the study.

Table 1 eCRF Data Collection

Variables	Enrollment visit	Post-enrollment follow-up visits
Informed Consent	**X**	**X**[1]
Demographics		
Age, gender, race/ethnicity, height	**X**	
Weight*	**X**	
Relevant Medical History		
Age at diagnosis of MF-CTCL	**X**	
Date of MF-CTCL diagnosis	**X**	
Method of diagnosis	**X**	
MF-CTCL TNMB classification*	**X**	
MF-CTCL TNMB classification change		**X**
MF-CTCL histology	**X**	
Malignancies and secondary malignancies	**X**	
Non-melanoma skin cancers	**X**	
Prior viral infections	**X**	
Atopic disorders	**X**	
Psoriasis	**X**	
Urticaria	**X**	
Mental disorders	**X**	
Family medical history	**X**	
Other relevant medical history	**X**	
Changes in medical history		**X**
Targeted MF-CTCL Treatments (Medication Use and Dosing)*†		
Valchlor	**X**	**X**
Other MF-CTCL treatments	**X**	**X**

Variables	Enrollment visit	Post-enrollment follow-up visits
Healthcare utilization related to MF-CTCL (as assessed by physician)		
Hospital admissions‡		**X**
Emergency room visits		**X**
Clinical Status (as assessed by physician)	**X**	**X**
Clinical Status Assessments*		
Composite Assessment of Index Lesion Severity	**X**	**X**
Modified Severity Weighted Assessment Tool	**X**	**X**
Physician's Global Assessment	**X**	**X**
Body Surface Area of disease	**X**	**X**
Patient-Completed Questionnaires§		
Visual Analogue Scale for pruritus	**X**	**X**
Skindex-29	**X**	**X**
Mycosis fungoides / Sézary syndrome-type cutaneous T-cell lymphoma	**X**	**X**
Safety Measures**		
AEs and SAEs	**X**+	**X**
Reports of secondary exposures		**X**^

*Included in pre-treatment data collection, which is performed at enrollment. All data must be completed as available.

†Includes collection of start and stop dates for each medication, including reasons for starting and stopping medications. Start and stop dates are also collected for Valchlor, including short gaps in treatment, such as drug holidays.

‡For each hospital admission, length of stay and primary admission and discharge diagnoses will be collected.

§To be completed by patients who can read and understand English and are able to self-complete the questionnaires based on the investigator's assessment. Patients who are unable to self-complete the questionnaires will not be excluded from the study.

**Safety measures, which include AEs and SAEs, will be collected from the informed consent date and prospectively at every visit during the study and up to 30-days post-discontinuation of Valchlor during the study. Ongoing AE and SAE data will be collected through the end of study, regardless of Valchlor use.

New AEs and SAEs that occur more than 30 days after discontinuation of Valchlor will be reported to Actelion US Drug Safety if investigator feels there is a possible causal relationship with Valchlor. Investigators are also expected to assess patients for AEs and SAEs and follow the appropriate reporting procedures per Section 7.

[+]All ongoing AEs and SAEs for patients being treated [see Section 5.2.1 for definition of "being treated"] with Valchlor.

[^]All reports of secondary exposures, as available, will be counted on the eCRFs. Additional information regarding secondary exposures will be forwarded directly to Actelion US Drug Safety via the Secondary Exposure Form. Refer to Section 7.1.1 for definition of secondary exposure.

AE = adverse event; eCRF = electronic Case Report Form; MF-CTCL = mycosis fungoides cutaneous T-cell lymphoma; SAE = serious adverse events; TNMB = tumor-node-metastasis-blood.

[1]Re-consent at the first follow up visit for subjects who are currently active in the study prior to Amendment 1.

5.3.1 Outcome definition and measures

The clinical outcomes and variables of interest for this study are clinical characteristics, treatment patterns, clinical status, as assessed by the physician (and the methods used in practice to assess clinical status), MF-CTCL-related healthcare utilization, as assessed by the physician (hospitalizations and emergency room visits), AEs and SAEs (e.g., dermatitis), and patient-completed symptoms and QOL questionnaires. Due to expected variability in practice patterns, no individual method of determining response, either at follow-up or in tandem with a prior assessment, is mandated and a subjective categorical assessment of response will be included in addition to quantitative measures of response, but assessments that do occur must be captured prospectively. Additionally, it is important to capture which methods were used pre-study, even where results may not be available, so that it is clear which assessments have a prior assessment that may have been considered in the physician's evaluation of response.

For patients who do not have any assessments, an affirmative response that the patient is still under care by the site will be requested quarterly so that the absence of reported assessments can be interpreted the same as the absence of actual assessments.

The following specific outcomes and variables of interest will be evaluated:

Clinical characteristics at enrollment and during study observation period.

Relevant medical history, including TNMB classification.

Use of prior MF-CTCL treatments.

Treatment patterns, including prescribing information, for the treatment of MF-CTCL (including dosing regimens, titration schemes, duration of time from initiation to discontinuation of therapy, and drug holidays for Valchlor).

Clinical status, as assessed by the physician (i.e., complete response, partial response,

stable disease, progressive disease, relapse).

Assessments (both whether or not the assessment was performed and the result of the assessment) used to define response, including, but not limited to:

- Composite Assessment of Index Lesion Severity.
- Modified Severity Weighted Assessment Tool.
- Physician's Global Assessment.
- Body Surface Area of disease.

Healthcare utilization related to MF-CTCL during the study period, as assessed by physician:

- Number of MF-CTCL-related hospitalizations.
- Number of MF-CTCL-related emergency room visits.

AEs and SAEs (e.g., dermatitis) whether or not related to Valchlor.

Patient-completed questionnaires:

- Visual Analogue Scale for pruritus (scale 0–10).
- Skindex-29.
- Mycosis fungoides / Sézary syndrome-type cutaneous T-cell lymphoma (MF/SS-CTCL).

5.3.2 Exposure definition and measures

Start of observation is defined as date of signed informed consent.

End of observation is defined as EOS, including death, withdrawal of consent, loss to follow-up, or study completion, whichever occurs first.

Total exposure time is defined as the date of first Valchlor exposure to the date of last Valchlor exposure.

Total on-study Valchlor exposure time is defined as the first day of Valchlor use to last day of Valchlor use during the observation period. If the patient was using Valchlor at end of observation, the last on-study day of Valchlor use is equal to the end date of observation period. Drug holidays are excluded from the sum of exposure time.

5.3.3 Covariate definition and measures

The following covariates will be considered for analyses as well as for exploring their relationship to safety-related (e.g., dermatitis) outcomes:

Age at enrollment, gender, race/ethnicity.

MF-CTCL medical history:

- Time since diagnosis and TNMB classification.

Medical history of previous and ongoing clinically significant underlying diseases and comorbid conditions.

Prior exposure to Valchlor and other MF-CTCL specific therapies.

5.4 Data sources

Data elements to be collected include the following: patient demographics, personal and family medical history, including MF-CTCL diagnosis date and etiology, current and historical MF-CTCL treatments, clinical status (as assessed by the physician), and which assessments were used to define response, MF-CTCL-related healthcare utilization (as assessed by the physician), AEs and SAEs whether or not related to Valchlor, deaths, patient-completed symptoms and QOL questionnaires. Table 1 provides an overview of the variables collected at enrollment and during the observation period [see Section 5.3.2 for definition]. For patients who do not have any visits, an affirmative response that the patient is still under care by the site will be requested quarterly, so that the absence of reported assessments can be interpreted the same as the absence of actual assessments.

Since this is a real-world, observational study, there are a number of sources of bias that could potentially affect any conclusions that may be drawn. The methods used to minimize these sources of bias in this study are detailed below [see Section 5.9].

Therapies specific to MF-CTCL during the course of this study are under the direction of the participating physician and not the study protocol. As this study collects data on both incident patients and prevalent patients, it is necessary to include the date of diagnosis in the data collection forms, in order to minimize potential survivor bias effect.

5.5 Study size

This study will have an approximate enrollment of 300 patients diagnosed with MF-CTCL who are being treated with Valchlor (newly initiated or continuing treatment).

A sample size of 270 evaluable patients is needed to estimate the percentage of patients with clinical status and the percentage of patients with hospitalizations, both with a margin of error of 6 percentage points. Assuming that up to 10% of patients may be non-evaluable due to incomplete follow-up, the sample size target for enrollment should be 300.

It is projected that approximately 200 evaluable patients will be re-consented under Amendment 1. The margin of error for 200 evaluable patients will be 7%.

Additionally, it is important to be able to estimate these same percentages with a margin of error of 10 percentage points or less for key subgroups representing a third or more of the patient population (e.g., patients newly initiating Valchlor). A total of 100 patients are required to achieve a margin of error of 10 percentage points per subgroup, so that a total enrollment of 300 patients is needed.

5.6 Data management

5.6.1 Data collection

Informed consent must be obtained prior to enrollment and data collection.

Re-consent must be obtained for patients that were enrolled in the study prior to Amendment 1 and still ongoing to complete 24 months of data collection from the enrollment date. Instead of the 12 months initially planned.

This study will collect data on MF-CTCL patients being treated with Valchlor [see Section 5.2.1 for inclusion criteria] under routine clinical care. This will include both data collected from assessments that are routinely performed for MF-CTCL patients being treated with Valchlor in clinical practice, and additional data from further assessments that may be performed.

No specific clinically mandated assessments are to be performed as part of study participation. Patient-completed questionnaires, however, are a study requirement and will be collected at all clinic visits during the study observation period. These questionnaires will be administered on paper by study coordinators. Patient clinical data (non-patient-completed) will be collected from the patient's medical records at enrollment and throughout the study period. All data will be entered into an eCRF at the time of collection or on a quarterly basis by study coordinators. AEs, reports of secondary exposure, and SAEs whether or not related to Valchlor will be entered into the eCRF at every visit and upon notification by the patient (e.g., reported via phone call).

A secure, Internet-based electronic data collection (EDC) system will be used for data entry and hosting. An audit trail will be maintained by the EDC system for all data entries and changes, indicating what entries/changes have been made, who made them, and when. Data will be encrypted when transferred over the Internet and will be stored in a secure database protected from unauthorized access.

All data collected will be de-identified before transmission to the central study coordinating center. Patient names will not be collected. Other patient identifiers will be collected in order to allow identification of study patients when SAEs are received by US Drug Safety outside of the study [see Section 7.4].

All SAE data entered into the Adverse Event (AE)/Adverse Drug Reaction (ADR) Form and all reports of secondary exposure will be transferred electronically and/or by fax by the physician to Actelion US Drug Safety to be processed in the Actelion Drug Safety Database. In addition, all AE data, reports of secondary exposure, and SAE data will be entered into the study eCRF.

5.7 Data analysis

5.7.1 Analysis sets and groups

Demographics and clinical characteristics will be summarized for all enrolled patients and also grouped separately for patients continuing treatment with Valchlor versus patients who are newly initiating Valchlor. Use of prior treatments and past methods of assessing response will be similarly analyzed separately for the two groups. The methods used for assessment of response (i.e., assessed with that method versus not assessed with that method, either at follow-up alone or in tandem with a prior assessment) will be reported as cumulative percentages over time and also as a percentage of first visits, second visits, etc. To minimize the potential impact of missing data, analyses will focus on variables that are available for all patients, such as whether a particular type of assessment occurred, rather than focusing on the results of a particular assessment. Analyses of response, based on a particular measure of response, will be limited to patients for whom that measure was reported. Therefore, patients with reported data will be compared to patients without any reported data with respect to demographics and pre-treatment clinical status to identify potential biases. The summary of response rates will be tabulated and the definition of response will be detailed in the Statistical Analysis Plan.

5.7.2 Clinical characteristics

Analyses of prior treatment, assessments, and relevant medical history will be summarized for all patients enrolled and also grouped separately for patients newly initiating Valchlor versus patients continuing on Valchlor. Percentages will generally be computed as a function of non-missing data; however, if a large amount of data are missing for some historical data, a comparison of patients with missing and non-missing data may be necessary to ensure generalizability based on non-missing data alone.

5.7.3 Treatment and assessment patterns

Because relatively little prospectively collected data is available on MF-CTCL treatment patterns, preliminary analysis will make use of patient listings to develop categories of treatment patterns. Categories will be developed without cross-referencing outcomes data to minimize bias (i.e., the focus will be the presence of specific assessments, not the test value associated with the assessment). Treatments individually and in combination will be reported in percentage terms, by visit, stratified by newly initiating patients and continuing patients to identify treatment patterns.

Duration of time from first post-initiation of Valchlor office visit to discontinuation of therapy will be assessed using Kaplan-Meier estimates of freedom from discontinuation. If short-term gaps in therapy are common, sensitivity analyses may be conducted in which these gaps do or do not count as treatment discontinuations, depending on the lengths of the gaps. These analyses will focus only on newly initiated patients.

5.7.4 Clinical outcomes

The main clinical outcomes that will be analyzed are clinical response, as assessed by the physician, and MF-CTCL-related healthcare utilization, as assessed by the physician (e.g., hospitalizations and emergency room visits). Rates of on-study hospitalization and emergency room visits will be computed as the ratio of utilization counts divided by on-study days. Hospitalization-free survival will be computed using Kaplan-Meier estimates.

Because a wide variation in assessments of clinical response is expected, the clinician's subjective evaluation of response will be summarized in addition to reporting the proportion of responses among patients for whom specific tests were performed. The subjective response will be cross-classified by which assessments were used. The summary of response data is primarily a descriptive analysis to better understand how and when physicians define response, and it does not represent an estimate of the efficacy of any MF-CTCL treatment.

5.7.5 Adverse events

The frequency and percentage of patients experiencing any on-study AEs, SAEs, or death will be summarized by system organ class and preferred MedDRA terminology. Additional detail for AEs of special interest (e.g., dermatitis) will be summarized separately. SAEs will be displayed in patient listings, both including and excluding events that were not concurrent with Valchlor exposure. The definition of an on-study event is one that occurs on the day of enrollment or later, but before the date of study discontinuation or completion.

5.7.6 Patient-completed questionnaires

The Skindex-29 is a questionnaire that results in three scales: emotions, symptoms, and functioning [Chren 1996, Chren 1997a, Chren 1997b, Chren 2001]. Appendix A shows the items in the Skindex-29 questionnaire and Appendix B describes the scoring of individual items to the 3 scales. To compute the scale, each item is first transformed to a linear 0–100 scale where responses of "Never", "Rarely", "Sometimes", "Often", and "All the time" are converted to values of 0, 25, 50, 75, and 100, respectively. Next, the mean of the non-missing items for each scale is computed to derive a scale score. Although missing data for individual items is allowed, no scale score will be computed if more than quarter of the items in the scale are missing.

The VAS for pruritus is a single value [Reich 2012] and is shown in Appendix C.

The MF/SS-CTCL questionnaire contains 12 questions [PatientsLikeMe 2016] and is shown in Appendix D.

At each study visit (1st, 2nd, etc.), the VAS for pruritus, the three scales of the Skindex-29 and the MF/SS-CTCL will be computed for patients who are and are not responders,

based on clinician assessment, at the time of that visit. These descriptive cross-sectional comparisons are intended to assess burden of disease in a Valchlor-treated cohort over time. The data related to all three questionnaires (VAS, Skindex-29, MF/SS-CTCL) will be collected on the QOL questionnaires.

5.8 Quality control

The use of the EDC system will allow for on-line data quality checks upon data entry. The EDC system will have pre-programmed automatic edit checks for data inconsistencies at the time of data entry, and resulting queries will be addressed by the site.

Site visits may be conducted by Actelion or by an authorized Actelion representative to inspect study data, patient medical records, and eCRFs.

No source data verification is mandated. However, the data will be reviewed on an ongoing basis for implausible data points, missing data points, assessments not conducted, and/or incomplete information. This review may result in queries to the sites. Centralized remote monitoring of patient data will be performed via the EDC tool. This approach will allow proactive monitoring and querying of data on an ongoing and regular basis with concentrated efforts on key data points (e.g., hospitalization, death, Valchlor interruption and discontinuation, AEs and SAEs, and secondary exposures) to encourage low rates of missing information. Communication with investigators and study coordinators will emphasize the importance of data entry completion. Analytical methods described in Section 5.7 will be applied to assess the extent of the missing data and the impact on inferential estimates.

5.9 Discussion of the study methods (including limitations)

This study is an observational, prospective study examining MF-CTCL patients being treated with Valchlor in a real-world clinical setting. Valchlor treatment will be based on prescriber decision and will not be influenced by participation in this study. The patients will be followed by their physician according to routine clinical practice. The study protocol does not mandate any treatment, procedures or visits. Patient-completed questionnaires, however, are a study requirement and will be administered at all study visits for patients who can read and understand English, and are physically and mentally able to complete the questionnaires based on the investigator's assessment.

Any interpretation of observational study results should consider limitations to observational real-world study designs, including potential sources of selection or information biases, and confounding factors.

To minimize selection bias, participating centers will offer enrollment in the study to all consecutive MF-CTCL patients currently treated with Valchlor [see Section 5.2.1 for inclusion criteria], regardless of other MF-CTCL specific therapy received before or at

the time of enrollment, or during the study. This study collects data on all users of Valchlor. At enrollment, a review of existing medical records will be performed to collect information as described per Table 1 (enrollment visit). Thereafter, all data will be collected during the observation period.

Patients who are enrolled under the original protocol prior to protocol Amendment 1 and are still ongoing in the study will be re-consented under Amendment 1 and will continue to follow the schedule of Table 1 eCRF Data Collection specified in this protocol up to end of study (Month 24). Patients who enrolled and have completed 1 year of the study under the original protocol will not be offered to continue in the study and thus not re-consented under Amendment 1.

To minimize the number of patients lost to follow-up, there will be regular contact with patients by the site, including 3 attempts to contact a patient before she/he is considered lost to follow-up.

6 PROTECTION OF HUMAN SUBJECTS AND ETHICAL APPROVAL

6.1 Institutional Review Board/Independent Ethics Committee approval

Depending on local regulations and the physician's institutional policies, and in compliance with local law, the physician may have to submit the study protocol, the form for the Patient Informed Consent, and other relevant information to an Institutional Review Board (IRB) / Independent Ethics Committee (IEC), local health authorities, data protection agency or others. Approval from the IRB/IEC must be obtained before going through a consent procedure with the patient and before entering data into the database. IRB/IEC information/approval must be documented in a letter to the physician, clearly identifying the study, the documents reviewed, and the date of approval.

6.2 Patient informed consent

The participating physician commits to obtaining approval for the Patient Informed Consent Form from his/her respective Research Ethics Board, if required by applicable site policies, national privacy regulations and other state and local laws relating to medical information, prior to commencement of the project. Moreover, if required, the participating physician will obtain a signed Patient Informed Consent Form from each patient (or legal guardian) whose data will be included in the project.

6.3 Patient confidentiality

By signing the protocol, the participating physician commits to complying with all related applicable local laws and regulations, including but not limited to the regulations in 45 CFR parts 160 and 164 (protected health information), such regulations also known as the "HIPAA Privacy Regulations".

7 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

With reference to collecting, processing and expediting of AE reports, Actelion as the sponsor of this prospective non-interventional study complies with international and national pharmacovigilance regulations.

7.1 Definitions

7.1.1 Adverse event or adverse experience

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

AEs include:

Recurrence or worsening of a pre-existing disease.

Increase in frequency or intensity of symptoms of a pre-existing disease or medical condition.

Continuous persistent disease or symptoms present at initiation of treatment or enrollment, which occurs first, that worsen following the start of the study.

Lack of efficacy in the acute treatment of a life-threatening disease Abnormal assessments, e.g., ECG, vital signs, or physical examination findings, if they represent a clinically significant finding that was not present at initiation of treatment or enrollment, which occurs first, or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of Valchlor.

Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which were not present at initiation of treatment or enrollment, which occurs first, or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of Valchlor.

In addition to AEs, exposure during pregnancy or lactation, product complaints, medication errors, overdose, misuse, abuse, occupational exposure and transmission of an infectious agent via Valchlor and the identification of a potential counterfeit medicinal product needs to be reported.

Reports of off-label use without an associated AE collected within non-interventional studies shall be included in final study reports.

Reports of inadvertent secondary exposure to the skin, mucous membranes, and eyes of individuals other than the patient being treated (e.g., patient’s caregiver or family member).

AEs do not include:

Medical procedures such as surgery, endoscopy, tooth extraction. However, the event that led to the intervention is considered an AE.

Situations in which no undesirable change occurred, such as hospitalization for cosmetic surgery or for social reasons.

7.1.2 Serious adverse events

An SAE is defined by the International Conference on Harmonisation guidelines as any AE fulfilling at least one of the following criteria:

Fatal.

Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.

Requiring inpatient hospitalization, or prolongation of existing hospitalization.

Resulting in persistent or significant disability or incapacity.

Congenital anomaly or birth defect.

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.

The following reasons for **hospitalizations** are exempted from being reported:

Hospitalizations for cosmetic elective surgery, or social and/or convenience reasons.

Hospitalization for pre-planned (prior to enrollment) standard monitoring of a pre-existing disease (present at enrollment) or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a patient with stable angina pectoris.

Hospitalizations for elective treatment of a pre-existing disease (present at enrollment) or medical condition that did not worsen, e.g., elective hip replacement for arthritis.

New AEs and SAEs that occur > 30 days after the discontinuation of Valchlor unless there is a reasonable possibility of causal relationship to Valchlor.

However, complications that occur during such hospitalizations are AEs or SAEs (for example, if a complication prolongs hospitalization) and must be reported as described below.

7.1.3 Relationship to the use of Valchlor

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

Related to Valchlor

This category applies to any AE (whether serious or not) that appears to have a reasonable possibility of causal relationship 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:

There is temporal relationship between the occurrence of the event and the administration of Valchlor.

The event abated (diminished) or disappeared when treatment with Valchlor was down-titrated, interrupted, or discontinued.

The event recurred when treatment was re-introduced.

Unrelated to Valchlor

This category applies to any AE (whether serious or not) that does not appear to have a reasonable relationship to the use of Valchlor (see above guidelines). Environmental factors such as clinical state and other treatments could equally have caused the event.

7.2 Secondary exposures, AE and SAE reporting to Actelion US Drug Safety

All reports of secondary exposures and all AEs will be recorded on the eCRFs and captured in the EDC clinical database. The AE data will be forwarded to Actelion US Drug Safety at predetermined intervals.

All SAEs (including secondary exposures) which occur after initiation of Valchlor treatment until 30 days after Valchlor discontinuation must be collected, recorded and reported during the study. New AEs and SAEs that occur more than 30 days after the discontinuation of Valchlor will be reported to Actelion US Drug Safety if the investigator assesses that there is a possible causal relationship with Valchlor. The minimum information required for collecting and forwarding an SAE to Actelion US Drug Safety is the product name, patient identifier, reporter contact information, and the identified SAE. All SAEs must be recorded on an AE/ADR Form. Cases of secondary exposure must recorded on the Secondary Exposure Form and submitted directly to Actelion US Drug Safety. The AE/ADR Form will be pre-populated with the information already entered in the eCRF, and it is the physician's responsibility to complete, print, and sign the form and forward to Actelion US Drug Safety directly, within 1 working day

of the investigator's first knowledge of the event, by fax or using the drug safety email address:

FAX: (866) 227-5886
Actelion US Drug Safety: drugsafetyUS@actelion.com

Actelion US Drug Safety will acknowledge the receipt of the AE/ADR form and provide a Manufacturer's Control Number (MCN – a unique number assigned by Drug Safety's database to the case) to the investigator and the Actelion Operations (Clinical Study Leader) within 48 hours. If no acknowledgement is received from Actelion US Drug Safety, the investigator must follow up immediately (or within 1 working day) with a phone call or email to Actelion US Drug Safety to ensure the AE/ADR Form has been received.

7.2.1 Follow-up of SAEs

Actelion US Drug safety will evaluate and process all safety reports received. If follow-up information is required, Actelion US Drug Safety will send a Data Clarification Form (DCF) directly to the investigator.

Follow-up information about a previously reported SAE must be reported directly to Actelion US Drug Safety via the AE/ADR Form within 1 working day of the investigator's first knowledge of the event.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

SAEs still ongoing at EOS must be followed up for 30 days after Valchlor discontinuation or until resolution or stabilization, or until the event outcome is provided, e.g., fatal outcome.

7.3 Reporting of pregnancy

Any pregnancy occurring during the administration of Valchlor, including the 30 days following product discontinuation, must be reported within 24 hours or 1 working day of the investigator's knowledge of the event.

Pregnancies must be reported by the investigator on the Actelion Pregnancy Form, which is faxed or forwarded via the above-mentioned Actelion US Drug Safety email addresses within 24 hours of the investigator's knowledge of the event.

Any pregnancy diagnosed in the female partner of a male subject during treatment with Valchlor must be reported to Actelion US Drug Safety within 24 hours of the investigator's knowledge of the event.

7.3.1 Follow-up of pregnancy

If subsequent follow-up information is required, Actelion US Drug Safety will send a DCF directly to the investigator.

Any pregnancy must be followed to its conclusion and its outcome must be reported to Actelion US Drug Safety directly.

7.4 Reconciliation

Actelion Operations (Clinical Study Leader) will keep a tracking log of all SAEs sent to Actelion US Drug Safety and the corresponding Actelion acknowledgement of receipt with Actelion MCN, so that reconciliation can be performed either periodically and/or at the end of the non-interventional study.

8 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Scientific Committee, in collaboration with Actelion, will publish data from this study at conferences and in journals when the sample size for analyses is sufficient.

9 DATA OWNERSHIP

Actelion Pharmaceuticals US, Inc. owns the data.

10 STUDY COMMITTEE(S)

An independent Scientific Committee of 4–6 key opinion leaders in the field of MF-CTCL has been appointed and their responsibilities will provide scientific input on the MF-CTCL Study protocol and review of study data.

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Appendix A Skindex-29 Questionnaire

Skindex29
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These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My skin hurts	☐1	☐2	☐3	☐4	☐5
2. My skin condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3. I worry that my skin condition may be serious	☐1	☐2	☐3	☐4	☐5
4. My skin condition makes it hard to work or do hobbies	☐1	☐2	☐3	☐4	☐5
5. My skin condition affects my social life	☐1	☐2	☐3	☐4	☐5
6. My skin condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7. My skin condition burns or stings	☐1	☐2	☐3	☐4	☐5
8. I tend to stay at home because of my skin condition	☐1	☐2	☐3	☐4	☐5
9. I worry about getting scars from my skin condition	☐1	☐2	☐3	☐4	☐5
10. My skin itches	☐1	☐2	☐3	☐4	☐5
11. My skin condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12. I am ashamed of my skin condition	☐1	☐2	☐3	☐4	☐5
13. I worry that my skin condition may get worse	☐1	☐2	☐3	☐4	☐5
14. I tend to do things by myself because of my skin condition	☐1	☐2	☐3	☐4	☐5
15. I am angry about my skin condition	☐1	☐2	☐3	☐4	☐5
16. Water bothers my skin condition (bathing, washing hands)	☐1	☐2	☐3	☐4	☐5
17. My skin condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18. I worry about side-effects from skin medications / treatments	☐1	☐2	☐3	☐4	☐5
19. My skin is irritated	☐1	☐2	☐3	☐4	☐5
20. My skin condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5

Please turn to next page

Skindex29 – United States/English – Original version
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Skindex29
©MMChren,1996

These questions concern your feelings over the past 4 week about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling.

HOW OFTEN DURING THE PAST 4 WEEK DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
21. I am embarrassed by my skin condition	☐1	☐2	☐3	☐4	☐5
22. My skin condition is a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23. I am frustrated by my skin condition	☐1	☐2	☐3	☐4	☐5
24. My skin is sensitive	☐1	☐2	☐3	☐4	☐5
25. My skin condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26. I am humiliated by my skin condition	☐1	☐2	☐3	☐4	☐5
27. My skin condition bleeds	☐1	☐2	☐3	☐4	☐5
28. I am annoyed by my skin condition	☐1	☐2	☐3	☐4	☐5
29. My skin condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5
30. My skin condition makes me tired	☐1	☐2	☐3	☐4	☐5

Appendix B Skindex-29 Scoring algorithm

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Education Information Dissemination

Scaling and Scoring Version 2.0: February 2012

Domains and Clusters

Skindex-29:

Domains	Number of Items	Cluster of Items	Item reversion	Direction of Domains
Emotions	10	3; 6; 9; 12; 13; 15; 21; 23; 26; 28	No	Higher score = higher impact of skin disease
Symptoms	7	1; 7; 10; 16; 19; 24; 27		
Functioning	12	2; 4; 5; 8; 11; 14; 17; 20; 22; 25; 29; 30		

Scoring of Domains

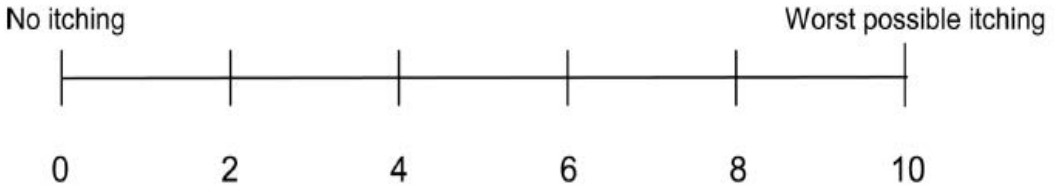
Skindex-29:

Item scaling	5-point Likert-type scale
Weighting of items	No
Range of scores	From 0 (no effect) to 100 (effect experienced all the time)
Scoring Procedure	All responses are transformed to a linear scale of 100. Transformed item scores: never = 0 rarely = 25 sometimes = 50 often = 75 all the time = 100 Scale scores: A scale score is the mean of a patient's responses to the items in a given scale. Note: Item 18 is a single item, not included in scoring.

Interpretation and Analysis of missing data	• If responses to more than 25% of items are missing overall, the questionnaire is eliminated. • If any scale has more than 25% of the responses missing, the scale is missing. • Scale scores are the average of non-missing items in a given scale.
Interpretation of multiple answers for one item	An item with multiple answers is considered missing.

Appendix C Visual Analog Scale for pruritus

Draw a line anywhere on the scale that best represents the severity of your itching:



Example:

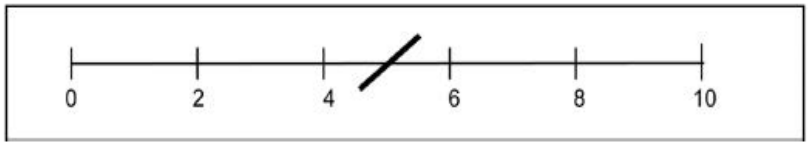


Fig 1.
Visual analogue scale.

Appendix D Mycosis fungoides/Sézary syndrome-type cutaneous T-cell lymphoma

The CTCL-QoL Final Version

Please complete these items regarding your experiences over the past 4 weeks.

In the past 4 weeks…

Q1…*how much did you worry that your mycosis fungoides or Sézary syndrome may get worse?*					
1 Not at all	2 A little bit	3 Somewhat	4 Quite a bit	5 Very much	
Q2. …*how often did you feel hopeless because of having mycosis fungoides or Sézary syndrome?*					
1 Never	2 Rarely	3 Sometimes	4 Often	5 Always	
Q3. …*how frustrated were you by the unpredictability of mycosis fungoides or Sézary syndrome?*					
1 Not at all	2 A little bit	3 Somewhat	4 Quite a bit	5 Very much	
Q4…*how often did you feel depressed or sad because of mycosis fungoides or Sézary syndrome?*					
1 Never	2 Rarely	3 Sometimes	4 Often	5 Always	
Q5…*how confident did you feel about managing your mycosis fungoides or Sézary syndrome?*					
1 Absolutely confident	2 Very confident	3 Moderately confident	4 Mildly confident	5 Not at all confident	
Q6. …*how severe were your mycosis fungoides or Sézary syndrome symptoms?*					
1 Not at all	2 A little severe	3 Somewhat severe	4 Severe	5 Very severe	☐ Does not apply (I don't have symptoms right now)
Q7. … *how burdensome was your mycosis fungoides or Sézary syndrome treatment?*					
1 Not at all burdensome	2 A little burdensome	3 Somewhat burdensome	4 Burdensome	5 Very Burdensome	☐ Does not apply (I don't have symptoms right now)
Q8. …*how much did your mycosis fungoides or Sézary syndrome limit your daily activities (work inside and outside of the house, self-care such as cooking, cleaning, getting dressed, etc.)?*					
1 Not at all	2 A little bit	3 Somewhat	4 Quite a bit	5 Very much	
Q9….*how often did mycosis fungoides or Sézary syndrome (the condition or associated treatment) leave you too tired to work or do daily activities?*					
1 Never	2 Rarely	3 Sometimes	4 Often	5 Always	
Q10. …*how much did mycosis fungoides or Sézary syndrome negatively affect your relationships with others close to you?*					
1 Not at all	2 A little bit	3 Somewhat	4 Quite a bit	5 Very much	
Q11. …*how often did you feel that others do not understand what you are going through with mycosis fungoides or Sézary syndrome?*					
1 Never	2 Rarely	3 Sometimes	4 Often	5 Always	
Q12… *to what extent did mycosis fungoides or Sézary syndrome make you feel uncomfortable being around people other than close family and friends?*					
1 Not at all	2 A little bit	3 Somewhat	4 Quite a bit	5 Very much	

Appendix E Mycosis fungoides/Sézary syndrome-type cutaneous T-cell lymphoma (CTCL QOL Scoring)

Scoring the CTCL-QoL

A total raw CTCL-QoL score is calculated by adding up the patient's total score from the 12 CTCL-QoL items. The *Raw to Scaled Score Conversion Table* provides scaled scores (M = 100, SD = 15) that correspond to the CTCL-QoL total score. Although total raw scores of 10 or 11 are possible due to two items with the response choice "Does not apply (I don't have symptoms right now)", these scores should not be interpreted differently from a score of 12. For scoring purposes, "Does not apply (I don't have symptoms right now)" is scored as a 0. Further, in order to score the CTCL-QoL, each of the 12 items must be completed.

Raw to Scaled Score Conversion Table

Raw CTCL-QoL Score	Scaled Score[1]	Raw CTCL-QoL Score, Continued	Scaled Score[1]
12 or below[2]	62	37	113
13	74	38	114
14	80	39	115
15	84	40	116
16	87	41	117
17	89	42	118
18	91	43	119
19	93	44	120
20	94	45	121
21	96	46	123
22	97	47	124
23	98	48	125
24	100	49	126
25	101	50	128
26	102	51	129
27	103	52	131
28	104	53	133
29	105	54	135
30	106	55	137
31	107	56	139
32	108	57	143
33	109	58	147
34	110	59 to 60	154
35	111		
36	112		

[1] Scaled scores were standardized on the current sample to have a mean of 100 and a standard deviation of 15

[2] While it is possible to obtain a raw score of 10 or 11 due to endorsing *"Does not apply (I don't have symptoms right now)"* to CTCL-QoL items, these scores should be viewed as equivalent to a 12.