**Title:** Statistical Analysis Plan for RD.03.SPR.104003, Amendment 1

Compound Name/Number: CD11301

Effective Date: 16DEC2019

Description: A randomized, double-blind, multi-center, placebo-controlled, parallel-arm, phase 2 trial to assess safety, efficacy, and pharmacokinetics of CD11301 0.03% and 0.06% gel in the treatment of Cutaneous T-Cell Lymphoma (CTCL), stages IA, IB, and IIA.

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## ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| BSA | Body Surface Area |
| CMH | Cochran–Mantel–Haenszel |
| COR | Common Odds Ratio |
| CR | Complete Response |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTCL | Cutaneous T-cell Lymphoma |
| ECG | Electrocardiogram |
| EU | European Union |
| FSFV | First Subject First Visit |
| ITT | Intent-to-Treat |
| LSFV | Last Subject First Visit |
| LSLV | Last Subject Last Visit |
| mCAILS | Modified Composite Assessment of Index Lesion Severity |
| mSWAT | Modified Severity-Weighted Assessment Tool |
| PGA | Patient Global Assessment of Improvement |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| PR | Partial Response |
| SAP | Statistical Analysis Plan |
| SI | International System of Units |
| TEAE | Treatment-Emergent Adverse Event |
| USA | United States of America |

## TRADEMARK INFORMATION

SAS SAS (Statistical Analysis Software) is a registered trademark of SAS Institute Inc.

## REVISION HISTORY

| Version | Date | Summary of revisions |
|---|---|---|
| 1.0 | 16DEC2019 | Initial version |
| 1.1 | 23APR2020 | Update for clarity on the multiplicity adjustment procedures, the per-protocol population definition, and multiple responses for SKINDEX. |

# 1. PURPOSE

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the findings of this study. It should be read in conjunction with the Clinical Study Protocol, RD.03.SPR.104003, V03, 25MAR2019. This SAP documents all changes and additions made to the analysis as presented in the protocol.

# 2. INTRODUCTION

This is a randomized, double blind, multi-center, placebo-controlled, three-arm parallel-group, trial in approximately 84 subjects with early stage CTCL. Subjects will be stratified by stage of disease and region (EU vs. USA) to ensure there are comparable numbers of subjects in each treatment arm of the trial.

The following treatments will be evaluated:

- resiquimod gel 0.03% (n=28),
- resiquimod gel 0.06% gel (n=28), and
- placebo gel (n=28) (only during cycle 1).

Subjects will undergo one treatment cycle of eight weeks on treatment followed by four weeks without treatment (cycle 1). The treatment will begin with applications three times per week (on non-consecutive days) for two weeks before increasing to five times per week for an additional six-week treatment period.

At Week 12, the active treatment arms will continue with an additional treatment cycle (cycle 2) similar to the first one (eight weeks with treatment, then four weeks without treatment). Subjects allocated to receive placebo in the first cycle will switch to receive active treatment with resiquimod gel 0.03% for their second treatment cycle.

After the completion of the second cycle, responder or stable subjects will be followed for 12 Weeks to assess duration of response and time to disease progression. After completion of Week 36 an analysis will be performed. Complete responders, as determined by the Investigator from the mSWAT Skin Involvement assessment at Week 36, will be followed to Week 72 or until relapse to assess time to relapse.

Rationale for this phase 2 trial is based on the results of a recent open label, investigator-initiated trial (IIT), which suggest benefit to patients with an acceptable safety profile. The data generated in the IIT support the further evaluation of resiquimod gel in the treatment of early-stage CTCL. The treatment effect, safety profile, final treatment regimen, and concentration will inform subsequent Phase 3 trial design.

# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1 STUDY OBJECTIVES

The aims of the trial are:

- to assess the efficacy and safety of two concentrations (0.03% and 0.06%) of resiquimod gel in the treatment of CTCL (stage IA, IB, or IIA) versus placebo,
- to compare and characterize the pharmacokinetic profile of two concentrations of resiquimod gel (0.03% and 0.06%) applied topically on up to 10% body surface area in subjects with early stage CTCL, and
- to assess a systemic effect of resiquimod gel on lesions distant from the treatment area(s).

## 3.2 STUDY ENDPOINTS

### 3.2.1 PRIMARY ENDPOINTS

- Subject overall response (complete or partial) of the target treated lesions at Week 12 based on the Modified Composite Assessment of Index Lesion Severity (mCAILS) score, imputing missing data as a non-response. Complete response (CR) is defined as an mCAILS score of 0; partial response (PR) is defined as a reduction in mCAILS score of at least 50%, but less than 100%, from Baseline.

### 3.2.2 SECONDARY ENDPOINTS

- Subject overall response (complete or partial) at Week 12 based on the Modified Severity-Weighted Assessment Tool (mSWAT) composite score, imputing missing data as a non-response. Complete response (CR) is defined as 100% clearance of skin lesions from Baseline. Partial response (PR) is defined as a reduction of skin lesions of at least 50%, but less than 100%, from Baseline, and a tumor subscore of zero (i.e. no tumor).
- Time to subject's first overall response (complete or partial) of the target treated lesions based on the mCAILS score.
- Duration of overall response (complete or partial) of the target treated lesions based on the mCAILS score.
- Time to first disease progression based on the mSWAT composite score.
- Change from Baseline in Skindex 29 survey results at Weeks 12, 24, and 36.

## 3.3 STATISTICAL HYPOTHESES

### 3.3.1 PRIMARY HYPOTHESIS

For the primary endpoint of response at Week 12 using the mCAILS composite score, the null hypothesis is that the common odds ratio (COR) comparing each treatment to placebo equals one. For each treatment:

$$H_0: COR = 1, H_A: COR \neq 1$$

### 3.3.2 MULTIPLE TESTING STRATEGY

The primary endpoint of overall response at Week 12 based on the mCAILS assessment will be tested first. The secondary endpoint of overall response at Week 12 based on mSWAT will be tested only if both treatment groups are statistically significant for the primary endpoint at 5%.

To account for testing multiple treatments, the Hochberg sequential testing procedure will be implemented to control the type I error rate at 5% for each of these primary and secondary tests (Hochberg, 1988).

The test of each endpoint will produce two p-values, one for each treatment compared to placebo. The larger of those two p-values will be compared to the significance level of 0.05. If significant, both p-values will be considered significant at the 0.05 alpha level and will be presented with 95% confidence intervals.

If the larger p-value is not significant, the smaller p-value will be compared to a significance level of 0.025 and presented with a 97.5% confidence interval.

For presentation purposes, p-values may be adjusted for the Hochberg procedure. If the larger p-value is greater than 0.05, the smaller p-value will be adjusted by multiplying it by two. If, after multiplying, the smaller p-value is then greater than the larger p-value, set it to the value of the larger p-value.

# 4. STUDY DESIGN

This is a randomized, double blind, multi-center, placebo-controlled, three-arm parallel-group, trial in approximately 84 subjects with early stage CTCL. Subjects will be stratified by stage of disease and region (EU vs. USA) to ensure there are comparable numbers of subjects in each treatment arm of the trial.

The following treatments will be evaluated:

- resiquimod gel 0.03% (n=28),
- resiquimod gel 0.06% gel (n=28), and
- placebo gel/resiquimod 0.03% gel (n=28) (placebo during cycle 1 and resiquimod 0.03% gel during cycle 2).

In order to capture the complete PK profile of resiquimod and its 5 metabolites, up to 36 subjects will be selected for full PK sampling at Weeks 12, 14, and 20.

Subjects will undergo one treatment cycle of eight weeks on treatment followed by four weeks without treatment (cycle 1). The treatment will begin with applications three times per week (on non-consecutive days) for two weeks before increasing to five times per week for an additional six-week treatment period. This dosing frequency will be reduced, if needed, based upon pre-defined dose adjustment rules (see Protocol Section 6.4). The treated area will be a maximum of 5% body surface area (BSA) as estimated via a Lund-Browder chart in this first cycle.

At week 12, the subjects in the active treatment arms will continue with an additional treatment cycle (cycle 2) similar to the first one (eight weeks with treatment, then four weeks without treatment). Subjects allocated to receive placebo in the first cycle will switch to receive active treatment with resiquimod gel 0.03% for their second treatment cycle. For each treatment arm during the second cycle, the treated area will be a maximum of 5% BSA for the first two weeks, then up to 10% BSA for the remaining six weeks.

Complete responders, who consent, will be followed from Week 36 to Week 72 or until relapse. During this period there will be no treatment, this is strictly observational.

The planned clinical trial duration, from first subject first visit (FSFV) to last subject last visit (LSLV), is approximately 32 to 34 months. The date of end of the clinical trial is defined as the date of LSLV. The planned duration of recruitment, from FSFV to last subject first visit (LSFV), is approximately 14 to 16 months. Clinical trial participation for each subject is up to 40 weeks, including an up to four-week screening phase. If they consent, subjects who are complete responders will have an additional follow up period of 36 weeks. See Appendix B for the full schedule of events. See Appendix C for the full list of inclusion and exclusion criteria.

To be included in the trial, subjects must have at least three distinct lesions, including one lesion on which no treatment will be applied but which will be selected to observe a potential remote (systemic) effect; this lesion will be referred to as the “target untreated lesion” throughout this SAP. Two to five lesions will be treated, and treatment effect will be specifically assessed on those lesions using the Modified Composite Assessment of Index Lesion Severity (mCAILS) score. These 2-5 lesions are called “target treated lesions” throughout this SAP.

The target untreated lesion is defined as a circumscribed, discrete lesion that should never receive treatment, preferably in a different anatomical region from treated target lesions, but regardless, at least 10cm away from other patches or plaques that will be treated with the trial drug; strict avoidance of cross-contamination will be required. In addition, during cycle 2 only, at the discretion of the investigator and up to the maximum allowed BSA, other lesions may be treated as long as all above requirements are fulfilled.

Progression of disease will result in discontinuation of the trial for the subject.

If a treated lesion is cleared (complete response according to the mCAILS assessment) at Week 12, it will not be treated during cycle 2. However, it will be followed up during cycle 2, and in case of lesion re-occurrence it will be treated with the trial drug for the remaining time of cycle 2.

After the completion of the second cycle, responder or stable subjects will be followed for 12 weeks to assess duration of response and time to disease progression.

If the subject is not a complete responder on mSWAT at Week 36, the subject will be discontinued from the study. For subjects with a Complete Response, as determined by the Investigator from the mSWAT Skin Involvement assessment at Week 36, subjects will be followed for an additional treatment-free 36 Weeks (extended follow-up). Should subjects relapse during this extended follow-up period; the subject will be early terminated from the study.

# 5. TIMING OF PLANNED ANALYSES

Two analyses will be performed:

- The first analysis will be performed after an interim database lock and unblinding when the last subject has completed Week 36. Details regarding which team members will stay blinded will be described in a communication plan by Galderma prior to this lock.
- The second analysis will be performed after full database lock when all subjects have completed Week 72 or discontinued the study. Specified Week 72 analyses will be done at this time, and identified analyses will be rerun to include data collected after Week 36.

Unless otherwise noted, all analyses detailed in this SAP will be performed at the Week 36 analysis. By-visit tables that summarize data before and after Week 36 will be run at both analyses. All tables and listings will be rerun at Week 72 to incorporate new data.

In the instance that all data, including extended follow-up data, is able to be locked by the time the last subject has completed Week 36, only one analysis will be run including all data. At Galderma's discretion, if the number of subjects entering extended follow-up are not sufficient to support the extended follow-up summaries, some summaries may be excluded; regardless, all data will be listed.

# 6. SAMPLE SIZE CONSIDERATIONS

Based on historical data, this phase 2 trial is powered using the following assumptions for dose response: 60% overall response rate on mCAILS at Week 12 with resiquimod gel versus 18% with placebo. The test statistic used is the chi-squared test of equal proportions.

In order to achieve at least 80% power to detect a significant difference between active and placebo, using a two-sided type I error of 0.025 (due to multiplicity adjustment), 25 subjects are needed in each arm for the primary efficacy analysis. Assuming a discontinuation rate of 10%, a total of 84 subjects (28 subjects per treatment arm) will be randomized.

# 7. ANALYSIS POPULATIONS

## 7.1 INTENT-TO-TREAT ANALYSIS POPULATION

The intent-to-treat (ITT) analysis population is defined as all subjects who are randomized. All efficacy analyses will be based on the ITT population. Analyses using the ITT population will be summarized using subjects' randomized treatment.

## 7.2 PER-PROTOCOL ANALYSIS POPULATION

The per-protocol (PP) population is defined as all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. The PP population will be used for the sensitivity analyses of primary and secondary efficacy endpoints. Analyses using the PP population will be summarized using subjects' randomized treatment. The PP population will be finalized prior to database lock.

## 7.3 SAFETY ANALYSIS POPULATION

The Safety population is defined as all subjects in the ITT population who applied the trial drug at least once. The Safety population will be used for the analysis of all safety data. Analyses using the Safety population will be summarized using subjects' actual treatment.

In the case of any subject taking an unplanned treatment, actual treatment will be assessed separately by period:

- For cycle 1, mis-dosed subjects will be summarized in the treatment group of the lowest dose of actual drug the subject applied during that period (either 0.03% or 0.06%), or Placebo if that is the only treatment taken.
- For cycle 2, subjects randomized to 0.03% or placebo/0.03% will be summarized in those treatment groups if they apply at least one dose of 0.03% drug; they will be summarized in the 0.06% group only if that's the only drug applied. Subjects randomized to 0.06% (who mis-dose, taking a dose of 0.03%) will be summarized in the 0.03% group.
- For follow-up and extended follow-up summaries, a subject's actual treatment during cycle 2 will be used.
- For overall summaries, a subject's actual treatment during cycle 2 will be used if available, otherwise their cycle 1 treatment will be used.

## 7.4 SAFETY EXTENDED POPULATION

The Safety Extended population is defined as all subjects in the Safety population that are documented as entering the extended follow-up period as collected on the CRF; these subjects have complete response based on mSWAT at Week 36 and have consented to enter Extended Follow-up. This population will be used for all Safety analyses for the Extended Follow-up period. Analyses using the Safety Extended population will be summarized using subjects' actual treatment.

## 7.5 PK ANALYSIS POPULATION

The PK population is defined as all subjects in the Safety population with complete PK profiles and no major protocol deviations which can influence the subject's evaluation of pharmacokinetics. Completeness of the PK profile will be assessed by Galderma prior to database lock and unblinding at Week 36. The PK population will be used for all PK summaries. Analyses using the PK population will be summarized using the subjects' actual treatment.

# 8. PROTOCOL DEVIATIONS

Determination of protocol deviations as major or minor will be done during blinded review prior to interim database lock and unblinding. Protocol deviations leading to exclusion from analysis populations will also be identified prior to database lock. Protocol deviations will be identified during the extended follow-up period; all deviations during this time will be considered minor. No protocol deviations will be programmatically identified.

Major protocol deviations that have a significant effect on efficacy will result in exclusion from the per-protocol population; major protocol deviations which can influence the subject's evaluation of pharmacokinetics will result in exclusion from the PK population.

Protocol deviations will be classified to a period based on the date of derivation as follows:

- Cycle 1: treatment start date – date of the Week 12 visit.
- Cycle 2: the day after the date of the Week 12 visit to the date of the Week 24 visit.
- Follow-up: the day after the date of the Week 24 visit to the day of the Week 36 visit.
- Extended follow-up: after the date of the Week 36 visit.

Deviations with missing or partially missing dates will not be classified to a period.

# 9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

## 9.1 BASELINE

Baseline is defined, unless otherwise noted, as the last available data on or prior to the date of first application of study drug.

## 9.2 STANDARD SUMMARY STATISTICS

Unless otherwise specified, summary of continuous measurements will include the mean, standard deviation, minimum, median, and maximum; summary of categorical measurements will include the counts and percentages for each category.

For non-pharmacokinetic summaries, means and medians will be presented to one more decimal place than the source data; standard deviations will be presented to two more decimal places than the source data; minimums and maximums will be presented to the same number of decimal places as the source data; percentages will be presented to one decimal place; confidence intervals will be presented to two decimal places; and p-values will be presented to four decimal places (p-value less than 0.0001 will be presented as <0.0001).

For pharmacokinetic summaries, concentrations and their summary statistics will be presented to three significant figures. %AUC, $T_{max}$, and $t_{1/2}$ values and their summary statistics will be presented to two decimal places (unless more are needed to present small values). $AUC_{0\text{-}24h}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ values and their summary statistics will be presented to three significant figures unless any individual value for a parameter is greater than or equal to 1000, in which case data for that parameter will be presented as integers. $C_{max}$ and $C_{trough}$ values and summary statistics will be presented to three significant figures.

## 9.3 STRATA AND COVARIATES

Subjects will be stratified during randomization by region (EU and USA) and stage of disease; for stage of disease there are two strata: either stage IA or stages IB and IIA combined.

CMH testing for the primary and secondary endpoints will stratify by stage of disease (IA and IB/IIA) and region (EU and USA), resulting in four strata (EU and IA, EU and IB/IIA, USA and IA, USA and IB/IIA). If the assumptions of the CMH test are not met, exact methods will be used using SAS® PROC LOGISTIC; a Mantel-Fleiss criterion value lower than 5 will determine the use of exact methods.

## 9.4 STATISTICAL SIGNIFICANCE

Each treatment (0.03% and 0.06%) group will be compared separately to the placebo treatment group using two-sided tests at an overall type I error rate of 0.05.

To account for testing multiple treatments, the Hochberg procedure will be implemented to control the type I error rate at 5%. See Section 3.3.2 for details.

## 9.5 EXAMINATION OF SUBGROUPS

The primary efficacy endpoint of subject overall response (complete or partial) of the target treated lesions at Week 12 based on the Modified Composite Assessment of Index Lesion Severity (mCAILS) score will also be summarized by the following subgroups:

- Region: EU, USA
- Baseline stage of disease: IA, IIA/IB
- Baseline disease type: mycosis fungoides, folliculotropic mycosis fungoides, other, not applicable
- Previous therapies for CTCL: phototherapy, chemotherapy, radiation, topical medication, combination therapy, none
- Age: less than 65 years old, greater than or equal to 65 years old
- Gender: female, male
- Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino

## 9.6 ANALYSIS OF CYCLES

For the purposes of analyses by cycle, the following date definitions will be used:

- The start of cycle 1 is defined as the date of the Baseline visit.
- The start of cycle 2 is defined as the date of the scheduled Week 12 visit if the subject has a CRF dispensation record at the Week 12 visit.
- The start of the follow-up period is defined as the date of the scheduled Week 24 visit if the subject does not discontinue the study at that visit.

- The start of the extended follow-up period is defined as the date of the scheduled Week 36 visit if the subject does not discontinue the study at that visit.

Efficacy summaries will present data in three columns:

- Summaries that contain data only from cycle 1 will display three treatment columns: 0.06%, 0.03%, and Placebo.
- Summaries that contain data from cycle 2, follow-up, or extended follow-up will display three treatment columns: 0.06%, 0.03%, and Placebo/0.03%.

Safety summaries will be presented with a separate table for each cycle. Overall summaries will present columns for 0.06%, 0.03%, Placebo/0.03%, and total. Cycle 1 summaries will present columns for 0.06%, 0.03%, and Placebo. Cycle 2 summaries will present columns for 0.06%, 0.03% (not including subjects in the Placebo/0.03% treatment group), Placebo/0.03%, and 0.03% Combined (defined as the total of the 0.03% and Placebo/0.03% treatment groups). Follow-up and extended follow-up summaries will present columns for previous use of 0.06%, 0.03%, Placebo/0.03%, and Total (defined as the total of all treatment groups).

For all summaries, Placebo represents vehicle treatment.

### 9.7 Unscheduled Visits

Unscheduled visits will be included when determining analysis visits for by-visit efficacy summaries. All unscheduled visits will be included in listings.

# 10. DATA HANDLING CONVENTIONS

## 10.1 Premature Withdrawal and Missing Data

The primary and secondary efficacy analyses of subject response based on the mCAILS and mSWAT composite score at Week 12 will be conducted treating missing data as a non-response.

These response rates will also be summarized at Weeks 24 and 36 treating missing data as a non-response.

## 10.2 Derived and Transformed Data

### 10.2.1 Study Population

#### 10.2.1.1 Demographics and Baseline Characteristics

Age group will be derived based on the age collected in the CRF. Subjects will be classified into two group: less than 65 years of age or greater than or equal to 65 years of age.

Region will be derived based on the country collected in the CRF. Subjects in the USA will be classified as USA, subjects from European countries will be classified as EU.

Classification for previous therapies for CTCL will be as follows:

- Phototherapy: previous procedure with high-level term of “Phototherapies”
- Chemotherapy: previous procedure with high-level term of “Chemotherapies”

- Radiation: previous procedure with high-level term of "Radiotherapies site unspecified" or "Skin radiotherapies"
- Topical medication: previous medication with level 2 ATC code of "D07" or level 4 ATC code of "L01AA," "D10AA," "C05AA," "D10AD," or "D06BB"
- Combination therapy: subject classified as more than one of the previous categories
- None: subject not classified into any category

Duration of CTCL in years will be calculated as:

(year of randomization) – (year of CTCL start date) + 1

CTCL start date will be determined from medical history with a lower-level term of "Cutaneous T-cell lymphoma."

#### 10.2.1.2 Previous and Concomitant Therapies and Procedures

Therapies and medications will be coded using the WHO-DD Enhanced v March 2017 dictionary. Procedures will be coded using MedDRA version 20.0.

Therapies and procedures will be classified as either previous, concomitant, and/or concomitant to the extended follow-up period. Previous therapies and procedures are those with an end date prior to the date of first dose of study drug; concomitant therapies and procedures are those with a start date on or prior to the date of the Week 36 visit (or if there is no Week 36 visit) and an end date on or after the date of first dose of study drug or those ongoing as of the date of first dose.

For subjects with an extended follow-up period start date, therapies and procedures with an end date after the date of the Week 36 visit, or those ongoing as of the date of the Week 36 visit, will be considered concomitant in the extended follow-up period.

Therapies and procedures with completely missing end dates will have their end date treated as ongoing for classification. Those with partially missing end dates will be imputed to be as late as possible given the non-missing portions of the date prior to classification.

Therapies and procedures with completely missing start dates will have their start date set to the therapy or procedure's end date or the subject's treatment start date, whichever is earlier (if the end date is partially missing, it will first be imputed following the above rule). Those with partially missing start dates will be imputed to be as early as possible given the non-missing portions of the date prior to classification.

Therapies and procedures with both a completely missing start and end date will be considered concomitant and concomitant to the extended follow-up.

#### 10.2.1.3 Medical History

Medical history will be coded using MedDRA version 20.0.

### 10.2.2 Efficacy Derivations and Classifications

#### 10.2.2.1 PRIMARY ENDPOINT

The mCAILS assessment total will be derived from components collected on the CRF. Target treated lesions (1-5 lesions) will be rated in erythema (0-8), scaling (0-8), plaque elevation (0-3), and size (0-18). These 4 ratings will be summed to create subtotals, one per lesion. The final mCAILS assessment score is the sum of these subtotals.

The percent change from Baseline at Week 12 will be calculated as:

((score at Week 12 – Baseline score) / Baseline score) * 100

Subjects with a percent change from Baseline at Week 12 of -100% (i.e., a Week 12 mCAILS score of 0) will be classified as complete response. Subjects without complete response (greater than -100%), but with a percent change from Baseline less than or equal to -50% will be classified as partial response.

A subject will be classified as a non-responder if the target lesions identified and assessed at Week 12 are not the lesions assessed at Baseline, or if any part of the target lesion data is missing at Week 12. For example, if a subject had four target lesions identified at Baseline, but at Week 12 only three of those lesions were assessed, they would be treated as a non-responder.

For the purposes of analyses in this SAP, all subjects with complete or partial response will be considered a responder.

#### 10.2.2.2 SECONDARY ENDPOINTS

**Subject overall response at Week 12 based on the mSWAT composite score**

The mSWAT composite score will be taken from the CRF. The percent change from Baseline at Week 12 will be calculated as:

((score at Week 12 – Baseline score) / Baseline score) * 100

Subject will be classified at Week 12 as follows:

- Complete response: Subjects with a percent change from Baseline at Week 12 of -100% will be classified with complete response.
- Partial response: Subjects without complete response (greater than -100%), but with a percent change from Baseline less than or equal to -50%, and with a tumor subtotal (collected from the CRF) of zero (i.e. no tumor), will be classified with partial response.
- Stable disease: Subjects with a percent change from baseline less than 25% and greater than -50%, and with a tumor subtotal of zero (i.e. no tumor), will be classified with stable disease.
- Progressive disease: Subjects with any of the following will be classified with progressive disease:
    - a percent change from baseline greater than or equal to 25%
        - exception: subjects classified at baseline as stage IA will only be classified with progressive disease if the affected body surface area (BSA) at that visit is greater than or equal to 10%, otherwise the subject will be classified with stable disease; affected BSA will be calculated as the sum of the patch,

plaque, and tumor subtotal of lesion BSA (prior to application of weighting factors) as collected in the mSWAT assessment
- a tumor subtotal of greater than zero
- classified with loss of response. Subjects with complete or partial response will be classified with loss of response if they have an increase in their mSWAT score greater than their nadir score plus half their baseline score. A subject's nadir score is their lowest mSWAT score collected up to, and including, the visit being assessed for loss of response (including Baseline and unscheduled visits).

For the purposes of analyses in this SAP, subjects with complete or partial response will be considered a responder.

**Time to subject's first overall response of the target treated lesions based on the mCAILS score**

For subjects randomized to 0.06% or 0.03% treatments, the time to a subject's first overall response (complete or partial) based on the mCAILS score will be calculated in days as:

(date of response) – (treatment start date) + 1

Subjects without response by Week 36 will be censored as of the date of their final visit or the Week 36 visit, whichever is earlier.

For subjects randomized to placebo, only data up to and including their scheduled Week 12 assessment will be considered. Placebo subjects without response, or with response after the start of cycle 2, will be censored as of the date of their Week 12 visit or final visit, whichever is earlier.

**Duration of overall response of the target treated lesions based on the mCAILS score**

For subjects randomized to 0.06% or 0.03% treatments, the duration of overall response (complete or partial) of the target treated lesions based on the mCAILS score will be calculated in days as:

(date of first non-response after responding) – (date of response) + 1

Subjects with no response will not be included in this analysis. Subjects continuing to respond (complete or partial response) at their final assessment or Week 36 will be censored as of that date, whichever is earlier. Duration will be calculated for each period of uninterrupted response, and the maximum uncensored period will be used in the analysis.

For subjects randomized to placebo, only data up to and including their scheduled Week 12 assessment will be considered. Placebo subjects continuing to respond at Week 12, or who show non-response after the start of cycle 2, will be censored as of the date of their Week 12 visit or final visit, whichever is earlier.

**Time to first disease progression based on the mSWAT composite score**

For subjects randomized to 0.06% or 0.03% treatments, the time to first disease progression based on the mSWAT composite score will be calculated in days as:

(date of progressive disease) – (treatment start date) + 1

Subjects with no progressive disease by Week 36 will be censored as of the date of their final visit or Week 36 visit, whichever is earlier.

For subjects randomized to placebo, only data up to and including their scheduled Week 12 assessment will be considered. Placebo subjects with no progressive disease at Week 12, or with progressive disease after the start of cycle 2, will be censored as of the date of their Week 12 visit or final visit, whichever is earlier.

**Change from Baseline in Skindex 29 survey results**

Subjects answer 30 questions as a part of the Skindex 29 survey. A composite score and three subscores will be calculated from the results. Item 18 of the survey is not used in any scoring.

First, answers to each item will be given a numeric value:

- Never = 0
- Rarely = 25
- Sometimes = 50
- Often = 75
- All the time = 100

If more than 25% of the items are unanswered (eight or more items), the composite score and all three subscores will be considered missing. If multiple responses are given at the same visit, the response with the higher numeric value will be used.

Each subscore is calculated as the average of the non-missing values for the answers to specific items. The items used to calculate each subscore are:

- Emotions: 3, 6, 9, 12, 13, 15, 21, 23, 26, and 28 (10 items)
- Symptoms: 1, 7, 10, 16, 19, 24, and 27 (7 items)
- Functioning: 2, 4, 5, 8, 11, 14, 17, 20, 22, 25, 29, and 30 (12 items)

If more than 25% of items within any subscore are unanswered, that subscore will be considered missing.

The composite score will be calculated as the average of the non-missing subscores.

Change from baseline will be calculated as:

(score at visit) – (score at Baseline)

### 10.2.3 Safety Derivations and Classifications

#### 10.2.3.1 Treatment Compliance and Exposure

**Treatment Duration**

Treatment duration will be calculated separately for each cycle and overall. For cycle 1, treatment duration is calculated as:

(date of last application of study drug during cycle 1) – (date of first application of study drug) + 1

For cycle 2, treatment duration is calculated as:

(date of last application of study drug during cycle 2) – (date of first application of study drug during cycle 2) + 1

Overall treatment duration is calculated as:

(date of last application of study drug) – (date of first application of study drug) + 1

Treatment start and end dates will not be imputed; if any are completely or partially missing, duration for that subject will be missing.

**Treatment Compliance**

Treatment compliance (%) will be calculated using the number of prescribed applications and the number of performed applications as entered into the CRF. The total number of prescribed applications will be summed overall and during each cycle. The total number of performed applications will be summed overall and during each cycle.

Treatment compliance will then be calculated overall and for each cycle as:

(number of performed applications / number of prescribed applications) * 100

**Medication Used in Grams**

Grams of medication used will be calculated per subject for cycle 1, cycle 2, and overall. Each subject's returned tube weight will be subtracted from their dispensed tube weight and totaled for

each summarized period. Medication usage will be summarized in the cycle during which the medication was dispensed.

As per Galderma's clinical supply process, the weight of each dispensed tube is assigned based on the average weight of a sample of kits from each batch. Hence, it is possible that some subjects are recorded as having returned more grams of drug than they were dispensed. If a subject's total medication usage is negative, it will be set to zero.

Returned medication that is not weighed (the data is missing, or the medication was damaged or unopened) will not be included in totals.

#### 10.2.3.2 ADVERSE EVENTS

Adverse events will be coded using MedDRA version 20.0.

An adverse event will be considered treatment-emergent if it occurs on or after the treatment start date.

Adverse events with missing onset dates will be considered treatment-emergent, unless recovered/resolved prior to the treatment start date. Adverse events with a partially missing onset date will be considered treatment-emergent unless the non-missing portion of the date definitively proves otherwise (i.e., if the onset date is set as late as possible given the non-missing portions of the date, it is still prior to treatment start), or if recovered/resolved prior to treatment start. For this classification, if the recovered/resolved date is completely missing it is considered ongoing, if it is partially missing it is considered as late as possible given the non-missing portions of the date.

Adverse events with onset dates prior to the treatment start date will be considered a pre-treatment adverse event.

Treatment-emergent adverse events will be classified to the cycle during which it occurred so as to be summarized separately by cycle and treatment group. This will be based on the event's onset date. The following date ranges will be used:

- Cycle 1: treatment start date – day prior to the date of the Week 12 visit.
- Cycle 2: the date of the Week 12 visit to the date of the Week 24 visit.
- Follow-up: the day after the date of the Week 24 visit to the day of the Week 36 visit.
- Extended follow-up: after the date of the Week 36 visit.

Overall summaries of adverse events will combine cycle 1, cycle 2, and follow-up.

A subject must have a start date for a cycle to have the event classified to that cycle. In the event an AE would be assigned to a cycle without a start date, it is assigned to the previous cycle.

For subjects in the 0.06% or 0.03% treatment groups, adverse events with completely missing onset dates will be classified as occurring during cycle 1. For subjects in the Placebo/0.03% treatment group, adverse events with completely missing onset dates will be classified as occurring during cycle 2, unless the subject has no cycle 2 start date, in which case they will be classified as cycle 1.

For subjects in the 0.06% or 0.03% treatment groups, adverse events with partially missing onset dates will have those dates imputed, prior to classification, to be as early as possible given the non-

missing portions of the date, but no earlier than the treatment start date. For subjects in the Placebo/0.03% treatment group, adverse events with partially missing onset dates will be classified to a cycle based on the non-missing portions of the onset dates and taking into account cycle 1, cycle 2, follow-up, and extended follow-up start dates; if the onset date could be in multiple cycles, the following priority will be followed: cycle 2, cycle 1, follow-up, extended follow-up. A subject must have a start date for a cycle to have an event classified to that cycle.

Adverse events with Common Terminology Criteria for Adverse Events (CTCAE) grade of 3 or 4 or those with missing severity data, will be considered severe. Adverse events indicated on the CRF of having a "reasonable possibility" of being related to the study drug or protocol procedure, or those with missing relationship data, will be considered related to the study drug or protocol procedure, respectively. Serious adverse events are those indicated as serious on the CRF.

Overall adverse event summaries will count each subject with an adverse event one time, even if that subject experienced multiple occurrences of the same adverse event. Adverse event summaries for a specific cycle will count each subject with an adverse event during that cycle one time even if that subject experienced multiple occurrences of the same adverse event during that cycle or the subject experienced that adverse event during a different cycle.

The maximum severity per subject per TEAE preferred term will be determined for each cycle. For summaries, subjects will be counted only once per cycle at the highest severity experienced.

For summaries of events with incidence >= 5%, the incidence rate will be determined separately for each cycle. Incidence rate for each treatment group will be calculated separately; the combined treatment groups are for presentation only and will not be used to calculate incidence.

**Time to Onset**

The time to onset of the first related TEAE, skin erosion TEAE, erythema TEAE, edema TEAE, flu-like symptoms TEAE, and ulceration TEAE for each subject during each cycle will be calculated.

- For cycle 1, only TEAEs with onset during cycle 1 will be considered, and time to onset will be calculated as the onset date minus treatment start date plus one. Subjects with no relevant event by their Week 12 visit will be censored at their Week 12 or final visit, whichever is earlier.
- For cycle 2, only TEAEs with onset during cycle 2 will be considered, and time to onset will be calculated as the onset date minus the cycle 2 start date plus one. Subjects with no relevant event by their Week 24 visit will be censored at their Week 24 or final visit, whichever is earlier.
- For follow-up, only TEAEs with onset during follow-up will be considered, and time to onset will be calculated as the onset date minus the follow-up start date plus one. Subjects with no relevant event by their Week 36 visit will be censored at their Week 36 or final visit, whichever is earlier.
- For extended follow-up, only TEAEs with onset during extended follow-up will be considered, and time to onset will be calculated as the onset date minus the extended follow-up start date plus one. Subjects with no relevant event by their Week 72 visit will be censored at their Week 72 or final visit, whichever is earlier.

- For the overall summary:
    - For the 0.03% and 0.06% treatment groups, all TEAEs during any cycle except extended follow-up are considered. Time to onset is calculated as the onset date minus treatment start date plus one. Subjects with no relevant event by their Week 36 visit will be censored at their Week 36 or final visit, whichever is earlier.
    - For the placebo/0.03% treatment group, two time to onsets will be calculated.
        - The first calculation will only consider TEAEs with onset during cycle 1, and will be calculated as the onset date minus treatment start date plus one; this will be presented in a "Placebo" column. Subjects with no relevant event by their Week 12 visit will be censored at their Week 12 or final visit, whichever is earlier.
        - The second calculation will only consider TEAEs with onset during cycle 2 or follow-up, and will be calculated as the onset date minus the cycle 2 start date plus one; this will be presented in a "Placebo/CD11301 0.03%" column. Subjects with no relevant event by their Week 36 visit will be censored at their Week 36 or final visit, whichever is earlier.
        - A subject's "first" TEAE is assessed for each of these time to onsets separately; a subject with an event during cycle 1 and a second event on or after start of cycle 2 would have two time to onsets calculated and be presented in both columns.

Events with completely or partially missing onset dates will not be considered in the calculation of time to onset.

**Duration of AEs**

The duration of skin erosion TEAEs, erythema TEAEs, edema TEAEs, flu-like symptoms TEAEs, and ulceration TEAEs will be calculated for each event. The duration of an AE will be calculated as the recovered/resolved date minus the onset date plus one. All events per subject will be averaged to produced one mean duration per TEAE preferred term of interest per subject.

Events with completely or partially missing onset dates will not be included in the calculation of mean duration.

For the Week 36 analysis:

If the recovered/resolved date is partially missing it will be imputed to be as late as possible given the non-missing portions of the date (but no later than the subject's discontinuation or Week 36 date). If the recovered/resolved date is completely missing, or is ongoing at the time the Week 36 analysis, it will be set to the Week 36 date or discontinuation date, whichever is earlier.

For the Week 72 analysis:

If the recovered/resolved date is partially missing it will be imputed to be as late as possible given the non-missing portions of the date (but no later than the subject's discontinuation or Week 72 date). If the recovered/resolved date is completely missing, or is ongoing at the time the Week 72 analysis, it will be set to the Week 72 date or discontinuation date, whichever is available.

#### 10.2.3.3 CLINICAL LABORATORY EVALUATIONS

Laboratory values will be summarized using SI units.

Laboratory values will be classified as low, normal, or high as compared to their low and high reference ranges.

### 10.2.4 OTHER EVALUATIONS

#### 10.2.4.1 INCIDENCE OF RELAPSE

Relapse is defined as any recurrence of disease (an mSWAT score greater than zero) in a subject with a previous assessment of complete response using the mSWAT composite score.

#### 10.2.4.2 TIME TO RELAPSE USING MSWAT SCORE DURING EXTENDED FOLLOW-UP

The time to a subject's relapse based on mSWAT score during the extended follow-up period will be calculated in days as:

(date of relapse) – (date of previous complete response) + 1

Only subjects with complete response at Week 36 will be included in this analysis, though the date of complete response could be earlier than Week 36 if the subject achieved complete response prior to Week 36. Subjects continuing to be a complete responder at discontinuation or Week 72 will be censored as of that date.

If a subject's date of complete response is partially missing, the latest possible date given the non-missing portion of the date will be used, but not to exceed the date of the subject's Week 36 visit. If a subject's date of first relapse is partially missing, the earliest possible date given the non-missing portion of the date will be used, but not earlier than the date of the subject's Week 36 visit.

#### 10.2.4.3 PHARMACOKINETIC PARAMETERS

The pharmacokinetic parameters for resiquimod and its five metabolites will be derived and sent to CRO for analysis. Details of the PK parameter derivations will be described in a separate PK analysis plan provided by Galderma. If the parameter cannot be estimated, it will be reported to CRO as Not Calculated (NC).

Two parameters, $AUC_{0\text{-}24h}$ and $C_{max}$, will be transformed using a natural logarithmic transformation prior to the statistical analysis.

Historical cutoffs will be used to handle presentation of PK concentrations and parameters. For descriptive summaries of concentrations:

- If more than 50% of subjects, by treatment, have a concentration value below the lower limit of quantification (LLOQ) at a summarized week/timepoint, that summary will be reported as Not Calculated (NC).
- If 50% or fewer subjects, by treatment, have a concentration value below the LLOQ at a summarized week/timepoint, all subjects with a value below the LLOQ will have their result imputed as 10 pg/mL prior to the calculation of summary statistics.

For descriptive summaries and statistical analysis of $AUC_{0\text{-}24h}$ and $C_{max}$ PK parameters:

- If more than 50% of subjects, by treatment, have the parameter value Not Calculated at a summarized week, that summary, and any statistical analysis including that week, will be reported as Not Calculated (NC).
- If 50% or fewer subjects, by treatment, have the parameter value Not Calculated at a summarized week, all subjects with a Not Calculated value will have their result imputed as 10.00 pg/mL (the limit of quantification) for $C_{max}$ and 240 pg*h/mL (the limit of quantification multiplied by 24 hours) for $AUC_{0\text{-}24h}$ prior to calculation of summary statistics or the statistical analysis.

For descriptive summaries of all other PK parameters:

- If more than 50% of subjects, by treatment, have the parameter value Not Calculated at a summarized week, that summary will be reported as Not Calculated (NC).
- If 50% or fewer subjects, by treatment, have the parameter value Not Calculated at a summarized week, that summary will be presented as normal and exclude all Not Calculated subjects.

For plots of the individual concentrations, concentrations below the lower limit of quantification will be imputed as 10 pg/mL. For plots of mean concentrations, week/timepoints reported in the table as Not Calculated (NC) will be plotted as 10 pg/mL. For listings of concentration data, the values below the limit of quantification will be listed as "BLQ." For listings of PK parameters, not calculated values will be listed as "NC."

## 10.3 Assessment Time Windows

By-visit efficacy summaries will use the analysis visit. The analysis visit will be assigned based on the cycle, study day, and endpoint.

Study day for cycle 1 will be calculated as the assessment date minus the date of first application of cycle 1 medication plus one; if the subject has no treatment start date, the randomization date will be used instead. Study day for cycle 2 will be calculated as the assessment date minus the date of first application of cycle 2 medication plus one. Study day for the follow-up period will be calculated as the assessment date minus the date of the nominal scheduled Week 24 visit plus one. Study day for the extended follow-up period will be calculated as the assessment date minus the date of the nominal Week 36 visit plus one.

All scheduled, unscheduled, and early termination visits will be assessed when determined windowed analysis visit. If multiple measurements are taken within the same window (as defined below), the one taken closest to the target study day will be used for the analysis. If two measurements are taken within the same window that are equally close to the target study day, the one taken on the scheduled visit will be used; if both are unscheduled or early termination visits, then the later of the two visits will be used.

Safety and pharmacokinetics data will not be windowed.

**Efficacy and Patient-Reported Parameter Visit Windows**

| Analysis Visit | Analysis Visit Number | Target Study Day | mSWAT and mCAILS | PGA | Skindex 29 | Pruritus | Stage of Disease |
|---|---|---|---|---|---|---|---|
| **Cycle 1: Day 1 to day of first dose of cycle 2** | | | | | | | |
| Baseline | 1 | 1 | <= 1 | NA | <= 1 | <= 1 | <= 1 |
| Week 2 | 2 | 15 | NA | NA | NA | 2 – 21 | NA |
| Week 4 | 3 | 29 | NA | NA | NA | 22 – 35 | NA |
| Week 6 | 4 | 43 | NA | NA | NA | 36 – 49 | NA |
| Week 8 | 5 | 57 | NA | NA | NA | 50 – 63 | NA |
| Week 10 | 6 | 71 | NA | NA | NA | 64 – 77 | NA |
| Week 12 | 7 | 85 | 2 – day of first dose in cycle 2 | 2 – day of first dose in cycle 2 | 2 – day of first dose in cycle 2 | 78 – day of first dose in cycle 2 | 2 – day of first dose in cycle 2 |
| **Cycle 2: Day of first dose of cycle 2 to scheduled Week 24 visit** | | | | | | | |
| Week 14 | 8 | 15 | NA | NA | NA | 2 – 21 | NA |
| Week 16 | 9 | 29 | NA | NA | NA | 22 – 35 | NA |
| Week 18 | 10 | 43 | NA | NA | NA | 36 – 49 | NA |
| Week 20 | 11 | 57 | NA | NA | NA | 50 – 63 | NA |
| Week 22 | 12 | 71 | NA | NA | NA | 64 – 77 | NA |
| Week 24 | 13 | 85 | 2 – date of Week 24 | 2 – date of Week 24 | 2 – date of Week 24 | 78 – date of Week 24 | 2 – date of Week 24 |
| **Follow-up: Week 24 visit to Week 36 visit** | | | | | | | |
| Week 28 | 14 | 29 | 2 – 42 | NA | NA | 2 – 42 | NA |
| Week 32 | 15 | 57 | 43 – 70 | NA | NA | 43 – 70 | NA |
| Week 36 | 16 | 85 | 71 – date of Week 36 | 2 – date of Week 36 | 2 – date of Week 36 | 71 – date of Week 36 | 2 – date of Week 36 |
| **Extended Follow-up: Week 36 visit to end of subject's participation** | | | | | | | |
| Week 40 | 17 | 29 | NA | NA | NA | 2 – 42 | NA |
| Week 44 | 18 | 57 | NA | NA | NA | 43 – 70 | NA |
| Week 48 | 19 | 85 | 2 – 126 | 2 – 126 | 2 – 126 | 71 – 98 | 2 – 126 |
| Week 52 | 20 | 113 | NA | NA | NA | 99 – 126 | NA |
| Week 56 | 21 | 141 | NA | NA | NA | 127 – 154 | NA |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Week 60 | 22 | 169 | 127 – 210 | 127 – 210 | 127 – 210 | 155 – 182 | 127 – 210 |
| Week 64 | 23 | 197 | NA | NA | NA | 183 – 210 | NA |
| Week 68 | 24 | 225 | NA | NA | NA | 211 – 238 | NA |
| Week 72 | 25 | 253 | >= 211 | >= 211 | >= 211 | >= 239 | >= 211 |

# 11. STATISTICAL ANALYSES AND METHODOLOGY

## 11.1 STUDY POPULATION

### 11.1.1 DISPOSITION OF SUBJECTS

Subjects screened, screen failed with reason for screen failure, randomized, treated, completed the study, temporarily discontinued treatment due to AE, and discontinued the study, along with reason for discontinuation from the study, will be summarized using planned treatment (and total) for all subjects. Randomized percentages will be based on the number of subjects screened; percentages for treated, completed, temporarily discontinued, and discontinued from the study subjects are based on the number of subjects randomized; and percentages for reasons for discontinuation from the study are based on the number of discontinued subjects.

For each period (cycle 1, cycle 2, follow-up, and extended follow-up) the number of subjects who completed the period, temporarily discontinued treatment during the period, and discontinued the study during the period, along with reason for discontinuation from the study, will be also be summarized. Percentages for completed and discontinued during a period will be based on the number of subjects randomized, percentages for reasons for discontinuation during the period are based on the number of subjects who discontinued during the period.

Screen failed subjects are defined as those subjects who are not randomized. Subjects are counted as having completed cycle 1 if they have a Week 12 visit. Subjects are counted as having completed cycle 2 if they have a Week 24 visit. Subjects are counted as having completed follow-up if they have a Week 36 visit. Subjects are counted as having completed extended follow-up if they have a Week 72 visit.

Subject disposition will also be summarized by site on the ITT population, which will not include screened or screen failure summaries.

These summaries of disposition and disposition by site will be run at both Week 36 and Week 72, with the extended follow-up summary only included at Week 72.

Counts of subjects in each analysis population will be summarized using planned treatment for the ITT and PP populations and actual treatment for the Safety, Safety Extended, and PK populations.

By-subject listings will summarize subject disposition (run at both analyses), subjects not meeting inclusion or exclusion criteria, and subject inclusion in analysis populations.

### 11.1.2 PROTOCOL DEVIATIONS

Major protocol deviations occurring prior to the extended follow-up period will be summarized by planned treatment on the ITT population. Major protocol deviations occurring prior to the extended follow-up period will also be summarized by site. All protocol deviations, major and minor, will be presented in a listing which will be run at both analyses.

### 11.1.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The following demographic and baseline characteristics information will be summarized using the ITT population:

- Age
- Age group (<65, >=65)
- Gender (Female, Male)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country
- Region (EU, USA)
- Skin phototype (Type I, Type II, Type III, Type IV, Type V, Type VI)
- Baseline weight (kg)
- Baseline height (cm)
- Baseline BMI ($kg/m^2$)
- Baseline BSA ($m^2$)

The following baseline disease characteristics will be summarized using the ITT population:

- CTCL stage (IA, IB/IIA)
- CTCL duration (years)
- Disease subtype (Mycosis Fungoides, Folliculotropic Mycosis Fungoides, Other, Not Applicable)
- Previous therapies for CTCL (Phototherapy, Chemotherapy, Radiation, Topical Medication, Combination Therapy, None)
- Number of target treated lesions
- BSA of target treated lesions ($cm^2$)
- BSA of target untreated lesions ($cm^2$)
- Baseline mCAILS – target treated lesions
- Baseline mCAILS – target untreated lesion
- Baseline mSWAT

Percentages for all demographics and baseline characteristics summaries will be based on the number of subjects with non-missing results. Demographics and baseline characteristics will be presented in a by-subject listing; additionally, information on childbearing potential will be presented in a separate listing. Target treated and untreated lesion locations and area will be presented in a listing.

### 11.1.4 Medical History and Previous and Concomitant Therapies and Procedures

Previous and concomitant therapies and procedures will be summarized using the ITT population, with percentages based on the ITT population totals; previous therapies and procedures for CTCL treatment and non-CTCL treatment will be summarized separately. Concomitant therapies and procedures occurring during the extended follow-up period will be noted as such in listings.

Preferred terms for drug names or procedures will be sorted by descending frequency in the resiquimod 0.06% treatment group within ATC fourth level coding or SOC; ATC and SOC codes will be sorted alphabetically.

Medical history and all therapies and procedures will be presented in by-subject listings; previous CTCL and non-CTCL therapies and procedures will be listed separately. Listings of concomitant therapies and procedures will be run at both analyses.

## 11.2 Efficacy Analyses

### 11.2.1 Primary Efficacy Analysis

The overall response rate and associated statistical testing of target treated lesions based on the mCAILS score at Week 12 will be summarized on the ITT population, with missing data imputed as a non-response.

This primary endpoint will also be summarized descriptively by subgroup on the ITT population using non-response imputation. The difference in rates from placebo, and associated 95% confidence intervals, for each subgroup will be presented on forest plots.

A CMH test will be used to analyze the number of responders. The CMH test will stratify by region (EU and USA) and stage of disease (IA and IB/IIA). The p-values from the general association statistic will be presented. If the data does not meet the assumptions of the CMH test (i.e. a Mantel-Fleiss criterion less than 5), exact methods will be used using SAS® PROC LOGISTIC.

The rate of overall response will be calculated as the number of responders divided by the total number of subjects in the population for each treatment. The difference in overall rate from placebo, and the standard error of that difference, will be presented. Confidence intervals around the difference from placebo will be calculated using the large-sample approximation for binary data without the use of a continuity correction. If it is found that there is insufficient data to meet the assumptions of the approximation, exact methods will be used instead.

Additionally, the strata-adjusted difference in proportion and confidence intervals will be presented (Kim, 2013). Weights will be calculated using the CMH method, and Newcombe confidence intervals will be reported.

Confidence intervals will be 95% or 97.5% depending on the results of the Hochberg adjustment.

This endpoint will also be summarized on the PP population using observed data as a sensitivity analysis; the rate for observed data will be calculated out of the number of subjects with a Week 12 assessment. The difference in rates from placebo and associated confidence intervals from the primary analysis and sensitivity analysis will be plotted on a forest plot.

The counts and percent of responders, as well as complete response and partial response separately, will also be summarized at Weeks 12, 24, and 36 using the ITT population, with missing data imputed as a non-response. This summary will be repeated on the PP population using observed data at Weeks 12, 24, and 36 (with percentages calculated out of the number of subjects with a response at the summarized analysis visit).

### 11.2.2 Secondary Efficacy Analyses

**Subject overall response at Week 12 based on the mSWAT composite score**

The response rate and associated statistical testing based on the mSWAT score at Week 12 will be summarized on the ITT, with missing data imputed as a non-response.

A CMH test will be used to analyze the number of responders. The CMH test will stratify by region (EU and USA) and stage of disease (IA and IB/IIA). The p-values from the general association statistic will be presented. If the data does not meet the assumptions of the CMH test (i.e. a Mantel-Fleiss criterion less than 5), exact methods will be used using SAS® PROC LOGISTIC.

The rate of response (overall, CR, and PR separately) will be calculated as the number of responders divided by the total number of subjects in the population for each treatment.

The difference in overall rate from placebo, and the standard error of that difference, will be presented. Confidence intervals around the difference from placebo will be calculated using the large-sample approximation for binary data without the use of a continuity correction. If it is found that there is insufficient data to meet the assumptions of the approximation, exact methods will be used instead.

Additionally, the strata-adjusted difference in proportion and confidence intervals will be presented (Kim, 2013). Weights will be calculated using the CMH method, and Newcombe confidence intervals will be reported.

Confidence intervals will be 95% or 97.5% depending on the results of the Hochberg adjustment.

This endpoint will also be summarized on the PP population using observed data as a sensitivity analysis; the rate for observed data will be calculated out of the number of subjects with a Week 12 assessment. The difference in rates from placebo and associated confidence intervals from the secondary analysis and sensitivity analysis will be plotted on a forest plot.

The counts and percent of responders, as well as complete response and partial response separately, will also be summarized at Weeks 12, 24, and 36 using the ITT population, with missing data imputed as a non-response. This summary will be repeated on the PP population using observed data at Weeks 12, 24, and 36 (with percentages calculated out of the number of subjects with a response at the summarized analysis visit).

Lastly, the counts and percent of subjects with complete response, partial response, stable disease, disease progression, and relapse will be summarized at Weeks 12, 24, 28, 32, and 36 using observed data on the ITT population. Additionally, shifts in these categories from Week 12 will be presented at Weeks 24, 28, 32, and 36; a “Missing” category will be included, and percentages will be based on the ITT population totals.

**Time to subject's first overall response of target treated lesions based on the mCAILS score**

The time to subject's first overall response of target treated lesions based on observed cases of the mCAILS score will be summarized using Kaplan-Meier estimates on the ITT population. The 25th, 50th, and 75th percentiles will be presented along with 95% confidence intervals using the log-log transformation. The p-value from the log-rank test will be presented. Kaplan-Meier graphs will also be presented.

**Duration of overall response of target treated lesions based on the mCAILS score**

The duration of overall response of target treated lesions based on observed cases of the mCAILS score will be summarized using Kaplan-Meier estimates on the ITT population. The 25th, 50th, and 75th percentiles will be presented along with 95% confidence intervals using the log-log transformation. The p-value from the log-rank test will be presented. Kaplan-Meier graphs will also be presented.

**Time to first disease progression based on the mSWAT composite score**

The time to first disease progression using observed cases of the mSWAT composite score will be summarized using Kaplan-Meier estimates on the ITT population. The 25th, 50th, and 75th percentiles will be presented along with 95% confidence intervals using the log-log transformation. The p-value from the log-rank test will be presented. Kaplan-Meier graphs will also be presented.

**Change from Baseline in Skindex 29 survey results**

Observed values and change from Baseline for the Skindex 29 survey will be summarized at Baseline and Weeks 12, 24, 36, 48, 60, and 72 on the ITT population. The composite score, as well as the subscores for Emotions, Symptoms, and Functioning will be summarized. In addition, items addressing fatigue and pruritus (items 1, 2, and 10) will be summarized separately.

As a sensitivity analysis, this summary will be repeated on the PP population for Weeks 12, 24, and 36. This sensitivity analysis will not include the summary of items 1, 2, and 10.

### 11.2.3 Other Efficacy Analyses

All efficacy endpoints will be presented in by-subject, by-visit listings, and will include all derived scores as well as components. Listings for mCAILS, mSWAT, and Skindex 29 Survey results will be run at both Week 36 and 72.

#### 11.2.4.1 Incidence of Relapse using mSWAT

The number of subjects with complete response will be summarized at Weeks 12, 24, 28, 32, and 36 on the ITT population. For each of those analysis visits (except Week 36), the number of subjects with complete response at that analysis visit who subsequently relapsed will be summarized by analysis visit out to Week 72; percentages will be based on the number of subjects with complete response at that analysis visit. This summary will be run at both analyses.

The same summary will be presented on the ITT population for subjects in extended follow-up at Weeks 36, 48, 60, and 72 and will be run only at the Week 72 analysis.

Subjects with relapse will be presented in a by-subject listing which will be run at both analyses.

#### 11.2.4.2 TIME TO RELAPSE USING MSWAT SCORE DURING EXTENDED FOLLOW-UP

The time to relapse using the mSWAT score during the extended follow-up period will be summarized using Kaplan-Meier estimates on the ITT population. The 25$^{th}$, 50$^{th}$, and 75$^{th}$ percentiles will be presented along with 95% confidence intervals using the log-log transformation. The p-value from the log-rank test will be presented.

Kaplan-Meier graphs will also be presented.

These analyses will only be run at the Week 72 analysis.

#### 11.2.4.3 PATIENT GLOBAL ASSESSMENT OF IMPROVEMENT (PGA)

The observed values for the PGA assessment will be summarized at Weeks 12, 24, 36, 48, 60, and 72 on the ITT population. PGA scores will be summarized categorically, with percentages based on the number of subjects with a PGA assessment at the summarized analysis visit.

PGA scores will be presented in a by-subject listing which will be run at both analyses.

#### 11.2.4.4 PRURITUS NUMERIC RATING SCALE

The observed values and change from Baseline for the pruritus numeric rating scale will be summarized as a continuous measurement at Baseline and Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72 on the ITT population. Average itch intensity and maximum itch intensity will be summarized separately.

Pruritus numeric rating scale results will be presented in a by-subject listing which will be run at both analyses.

#### 11.2.4.5 STAGE OF DISEASE

Stage of disease will be summarized categorically by analysis visit, with percentages out of the number of subjects with an assessment at the summarized analysis visit. Shifts from Baseline in the classification of CTCL disease as IA, IB, and IIA will be presented at Weeks 12, 24, and 36on the ITT population. A "Missing" category will be included, and percentages will be based on the ITT population totals.

Stage of disease classification will be presented in a by-subject listing which will be run at both analyses.

## 11.3 SAFETY ANALYSES

### 11.3.1 TREATMENT COMPLIANCE AND EXPOSURE

Treatment duration will be summarized descriptively on the Safety population overall and for each cycle.

Total number of performed applications, total number of prescribed applications, total prescribed dose, total number of missed applications, total number of missed applications due to dose modification, treatment compliance, and total used grams will be summarized descriptively overall and for each cycle of the Safety population.

Treatment duration, prescribed and performed applications and dose information, and compliance will be presented in a by-subject listing. Drug dispensation and accountability will be listed separately.

Kit information, including number, dispensed data, and the treatment of the kit will be listed.

### 11.3.2 ADVERSE EVENTS

All summaries of treatment-emergent adverse events will be presented on the Safety or Safety Extended populations using MedDRA version 20.0 coding. For overall summaries, percentages will

be based on the number of subjects per treatment in the Safety population; for summaries specific to a period, percentages will be based on the number of subjects at risk during the summarized period (for extended follow-up summaries, this is the Safety Extended population).

Subjects will be considered at risk during a cycle if they have a start date for that cycle as defined in Section 9.6, with the exception that the start of cycle 1 is considered treatment start date instead of the Baseline visit.

The following summaries will be produced by system organ class (SOC) and preferred term (PT). These summaries will be sorted alphabetically by system organ class, with preferred terms sorted within system organ class in descending order by percentage in the resiquimod 0.06% treatment group, breaking ties with the placebo treatment group. These summaries will be presented for each period (cycle 1, cycle 2, follow-up, and extended follow-up). Additionally, the summary of TEAEs will be presented overall.

- Treatment-emergent adverse events (TEAEs)
- TEAEs with incidence >= 5% in any treatment group
- Serious TEAEs
- Serious TEAEs related to the investigational product
- Severe TEAEs (TEAEs with CTCAE grade of 3 or 4)
- Severe TEAEs related to the investigational product
- TEAEs related to the investigational product
- TEAEs by CTCAE severity grade (maximum grade for subject counts)
- TEAEs leading to discontinuation from the study or investigational product (IP)
- Related TEAEs leading to discontinuation from the study or IP
- TEAEs leading to dose frequency reduction or temporary discontinuation
- TEAEs of application site reactions (preferred terms of “Application and instillation site reactions” and “Administration site reactions NEC”)
- TEAEs of Skin Erosion, Erythema, Edema, Flu-like Symptoms, and Ulceration

Additionally, summaries of TEAEs and TEAEs related to the investigational product will be presented by preferred term, with preferred terms sorted in descending order by percentage in the resiquimod 0.06% treatment group.

All summaries by SOC/PT or by PT will include counts of total events as well as counts of subjects experiencing those events.

An overall summary of adverse events will present adverse event counts in each of the above categories, as well as TEAEs related to the protocol procedure, cutaneous TEAEs, cutaneous TEAEs related to investigational product, and deaths. This overall summary will be presented overall (up to Week 36) and for each period.

For specific event summaries, the following preferred terms will be used:

| **Summary** | **Preferred Terms** |
|---|---|
| Skin Erosion | Skin erosion, Application site erosion, Administration site erosion |

| | |
|---|---|
| Erythema | Erythema, Application site erythema, Administration site erythema |
| Edema | Skin oedema, Application site oedema, Administration site oedema |
| Flu-like Symptoms | Influenza like illness |
| Ulceration | Skin ulcer, Application site ulcer, Administration site ulcer |

The time to onset of the first related TEAE, first skin erosion TEAE, first erythema TEAE, first edema TEAE, first flu-like symptoms TEAE, and first ulceration TEAE will be summarized using a Kaplan-Meier analysis; the number of subjects with an event, number of censored subjects, and the 25$^{th}$, 50$^{th}$, and 75$^{th}$ percentiles will be displayed. This will be done by cycle and overall. The overall summary will include all TEAEs occurring during the study up to Week 36, however, a column for placebo will only present TEAEs occurring during cycle 1 (using treatment start date to calculate time to onset) and a column for placebo/0.03% will only present TEAEs occurring after cycle 1 (using cycle 2 start date to calculate time to onset). The by-cycle summaries will only include TEAEs occurring during the summarized cycle, and will use treatment start date (for cycle 1) or cycle start date (for cycle 2, follow-up, and extended follow-up) when calculating time to onset; only subjects with a start date for the summarized cycle will be included in that cycle's analysis.

The mean (per subject) duration of skin erosion TEAEs, erythema TEAEs, edema TEAEs, flu-like symptoms TEAEs, and ulceration TEAEs will also be summarized by cycle. The summaries will present descriptive statistics on the mean durations of all TEAEs with onset dates (imputed if necessary) during that cycle. All mean duration summaries will be run at both the Week 36 and Week 72 analyses to capture durations of events ending after Week 36.

Separate by-subject listings will present adverse event data for TEAEs, serious TEAEs, severe TEAEs, TEAEs related to the investigational product, TEAEs leading to discontinuation, deaths, and pre-treatment adverse events. All TEAE listings will be run at both the Week 36 and Week 72 analyses.

### 11.3.3 Clinical Laboratory Evaluations

The following laboratory parameters will be summarized:

Blood Chemistry

- ALT
- Albumin
- Alkaline phosphatase
- AST
- Bicarbonate
- Bilirubin direct
- Blood urea nitrogen
- Chloride
- Creatinine
- Gamma glutamyl transferase
- Glucose

- Potassium
- Sodium
- Total bilirubin
- Triglycerides
- Uric acid

Hematology:

- Basophils
- Eosinophils
- Erythrocytes
- Hematocrit
- Hemoglobin
- Leukocytes
- Lymphocytes
- Mean cell volume
- Monocytes
- Neutrophils
- Platelets
- Reticulocyte percent
- International Normalized Ratio (INR)

Urinalysis

- Glucose
- Ketones
- Specific gravity
- Blood
- pH
- Protein
- Urobilinogen
- Nitrite
- Leukocytes

Thyroid Function Test

- Thyroid stimulating hormone (TSH)
- T3
- T4
- Thyroid peroxidase
- Thyroglobulin antibodies

Blood chemistry and hematology laboratory parameters will be summarized separately using descriptive statistics on the Safety population for cycle 1, cycle 2, and follow-up and the Safety Extended population for extended follow-up. Additionally, percent change will be presented for

neutrophils, lymphocytes, eosinophils, monocytes, and basophils. The following visits and summaries will be presented:

- Cycle 1 summaries (Safety population):
  - Baseline observed
  - Weeks 2, 8, and 12 observed
  - Weeks 2, 8, and 12 change from baseline
- Cycle 2 summaries (Safety population):
  - Baseline observed
  - Week 12 observed
  - Weeks 14, 20, and 24 observed
  - Weeks 14, 20, and 24 change from baseline
  - Weeks 14, 20, and 24 change from Week 12
- Follow-up summaries (Safety population):
  - Baseline observed
  - Week 12 observed
  - Week 24 observed
  - Week 36 observed
  - Week 36 change from baseline
  - Week 36 change from Week 12
  - Week 36 change from Week 24
- Extended Follow-up summaries (Safety Extended population):
  - Week 36 observed
  - Weeks 48, 60, and 72 observed
  - Weeks 48, 60, and 72 change from Week 36

The observed values and change from Baseline in thyroid function test parameters will be summarized at Baseline and Weeks 8 and 20.

Urinalysis parameters will be summarized categorically by visit, with percentages based on the number of subjects with data at the summarized visit.

Shifts in classification of laboratory parameters as low, normal, and high will be presented for each visit for hematology and blood chemistry, separated by period. Shifts in the classification of laboratory parameters as normal, abnormal and clinically significant, and abnormal and not clinically significant will be presented for each visit for hematology, blood chemistry, and urinalysis, separated by period. The following shifts will be presented:

- Cycle 1 summaries (Safety population):
  - Shift from baseline to Weeks 2, 8, and 12
- Cycle 2 summaries (Safety population):
  - Shifts from baseline to Weeks 14, 20, and 24
  - Shifts from Week 12 to Weeks 14, 20, and 24
- Follow-up summaries (Safety population):
  - Shifts from baseline to Week 36
  - Shifts from Week 12 to Week 36

- Shifts from Week 24 to Week 36
- Extended Follow-up summaries (Safety Extended population):
  - Shifts from Week 36 to Weeks 48, 60, and 72

Shifts from Baseline of classification of thyroid function tests as normal, abnormal and clinically significant, and abnormal and not clinically significant will be summarized at Week 8 and Week 20. A "Missing" category will be included on all shift tables, and percentages will be based on the population totals.

All laboratory results will be presented in by-subject listings. All laboratory results for subjects with at least one abnormal laboratory result will be presented in separate listings and flagged if clinically significant. Separate listings will present all laboratory results for subjects with at least one clinically significant laboratory result. Listings for hematology, blood chemistry, and urinalysis parameters will be run at both Week 36 and 72.

### 11.3.4 VITAL SIGNS AND WEIGHT

Pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, and weight will be summarized descriptively. Summaries of cycle 1, cycle 2, and follow-up will use the Safety population; the extended follow-up summary will use the Safety Extended population.

- Cycle 1 summaries (Safety population):
  - Baseline observed
  - Weeks 2, 4, 8, and 12 observed
  - Weeks 2, 4, 8, and 12 change from baseline
- Cycle 2 summaries (Safety population):
  - Baseline observed
  - Week 12 observed
  - Weeks 14, 16, 20, and 24 observed
  - Weeks 14, 16, 20, and 24 change from baseline
  - Weeks 14, 16, 20, and 24 change from Week 12
- Follow-up summaries (Safety population):
  - Baseline observed
  - Week 12 observed
  - Week 24 observed
  - Week 28, 32, and 36 observed
  - Week 28, 32, and 36 change from baseline
  - Week 28, 32, and 36 change from Week 12
  - Week 28, 32, and 36 change from Week 24
- Extended Follow-up summaries (Safety Extended population):
  - Week 36 observed
  - Weeks 48, 60, and 72 observed
  - Weeks 48, 60, and 72 change from Week 36

All vital signs and weights will be presented in a by-subject listing. All vital signs for subjects with at least one clinically significant vital sign will be presented is a separate listing. Listings will be run at both the Week 36 and Week 72 analyses.

### 11.3.5 ELECTROCARDIOGRAM (ECG)

Subjects with at least one abnormal ECG result will be presented in a by-subject listing; subjects with at least one clinically significant ECG result will be presented in a separate listing. Subjects with at least one abnormal serial ECG result will be presented in a separate by-subject listing; subjects with at least one clinically significant serial ECG result will be presented in a separate listing.

### 11.3.6 PHYSICAL EXAMINATIONS

Subjects with at least one abnormal physical examination result will be presented in a by-subject listing.

### 11.3.7 OTHER SAFETY ANALYSES

Pregnancy tests (urine and serum) and patch tests for suspected allergic contact reactions will be presented in by-subject listings.

## 11.4 PHARMACOKINETICS

The observed pre-dose concentrations will be summarized descriptively (using n, mean, SD, coefficient of variation, geometric mean, geometric CV, median, minimum, and maximum) by analyte (CD11301, S-28371, S-31451, S-32483, S-32899, and S-32544), treatment, and visit. This summary will be done using all collected pre-dose PK concentrations for the Safety population.

Observed concentrations at all collected time points will be summarized similarly on the PK population.

The following pharmacokinetic parameters will be summarized descriptively (using n, mean, SD, coefficient of variation, geometric mean, geometric CV, median, minimum, and maximum) at Weeks 12, 14, and 20 on the PK population by analyte: $C_{max}$, $T_{max}$, $C_{trough}$, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $t_{1/2}$, and %AUC.

Additionally, resiquimod (CD11301) $AUC_{0\text{-}24h}$ and $C_{max}$ will be analyzed using an analysis of variance (ANOVA). For both parameters, the individual parameter values will be transformed with a natural logarithmic transformation prior to analysis. Two analyses will be done separately for each parameter:

1. For each treatment group, an ANOVA model will be run with week and subject as factors. A 90% confidence interval will be computed for the difference in arithmetic means between each pairwise timepoint (week). These limits will then be exponentiated to obtain the confidence intervals of the ratio of geometric means between each time point in the original scale. Earlier weeks will be subtracted from later weeks, meaning ratios greater than 1 will mean a higher geometric mean at the later week. The model will be run three times, comparing respectively Week 20/Week 14, Week 20/Week 12, and Week 14/Week 12 data. Each run will be conducted excluding the data from the week that is not relevant for the comparison in question.
2. For each week, an ANOVA model will be run with treatment as the factor. A 90% confidence interval will be computed for the difference in arithmetic means between each pairwise treatment. These limits will then be exponentiated to obtain the confidence intervals of the

ratio of geometric means between each treatment in the original scale. Lower doses (with Placebo being considered lower than 0.03%) will be subtracted from higher doses, meaning ratios greater than 1 will mean a higher geometric mean for the higher dose. The model will be run three times, comparing respectively 0.06%/0.03%, 0.06%/Placebo, and 0.03%/Placebo data. Each run will be conducted excluding the data from the treatment that is not relevant for the comparison in question.

Individual subject concentrations, and mean concentrations, will be plotted by time for each analyte, treatment, and visit on both a linear and semi-logarithmic base 10 scale (i.e., observed concentrations plotted on the observed scale and a log base 10 scale). All PK figures will be presented on the PK population.

The individual PK concentrations will be presented in a listing by analyte, treatment, subject, visit date, and sampling time on the Safety population.

The individual PK parameters will be presented in a listing by analyte, treatment, subject, and visit date on the PK population.

# 12. CHANGES FROM PLANNED ANALYSIS

The protocol outlines a last-observation-carried-forward (LOCF) sensitivity analysis for mCAILS, mSWAT, and Skindex 29 Survey results. These analyses were removed due to the fact that data for these parameters is collected infrequently enough that there would be no visits to pull forward, resulting in an analysis not significantly different from the missing-as-non-response analysis.

# 13. REFERENCES

Hochberg, Y. (1988). A Sharper Bonferroni Procedure for Multiple Significance Testing. *Biometrika*, *75*, 800–803.

Kim, Y., Won S. (2013). Adjusted proportion difference and confidence interval in stratified randomized trails. *PharmaSUG 2013, Paper SP04.*