CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.03.SPR.104003

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TITLE PAGE

Title: A randomized, double-blind, multi-centre, 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		
Project Name or CD number: CD11301	**Project Number:** 392	**Clinical Trial Phase:** *2*

EUDRACT NUMBER 2017-001677-16
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For any safety questions, please contact the Clinical Safety Officer (CSO) using the contact details provided in Section 7.2.4.2.2

For any medical questions related to the clinical trial protocol, please contact the Medical Expert (see contact details in trial team contact list).

COORDINATING INVESTIGATOR:

Name and Title:	PPD , MD, Coordinator Investigator
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This clinical trial will be performed in compliance with applicable regulatory requirements and Good Clinical Practice (GCP). This clinical trial protocol follows guidelines outlined by the International Conference on Harmonisation (ICH) and the Galderma template.

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Clinical Trial Title: A randomized, double-blind, multi-centre, 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	
Short Title: Safety, efficacy and pharmacokinetics of CD11301 gel in early stage CTCL	
Clinical Trial Phase: 2	**Clinical Trial Population:** adults aged 18 years or over, who have a diagnosis of CTCL (stage IA, IB, or IIA) confirmed by clinical examination, relevant laboratory testing, imaging and biopsy examinations.
Clinical Trial objectives:	▪ To assess the efficacy and safety of two concentrations (0.03% and 0.06%) of resiquimod gel (CD11301 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 (BSA) in subjects with early stage CTCL. ▪ To assess a systemic effect of resiquimod gel on lesions distant from the treatment area(s).
Clinical Trial design:	Randomized, double blind, multi-centre, placebo-controlled, three-arm parallel-group trial in subjects with early stage CTCL. The following treatments will be evaluated: - resiquimod gel 0.03% - resiquimod gel 0.06% - placebo gel (only in Cycle 1, then resiquimod gel 0.03% in Cycle 2) Subjects will be stratified by stage of disease, to ensure there are comparable numbers of subjects in stage IA and in stage (IB+IIA) in each of the active treatment arms and placebo arm of the trial. Stratification will also be attempted by region if possible (EU vs USA). There will be 2 treatment cycles, each of which followed by a 4-Week treatment-free period: - Cycle 1: subjects will be treated with placebo gel, resiquimod gel 0.03% or resiquimod gel 0.06% for 8 Weeks: 3 times per Week for 2 Weeks, on nonconsecutive days, on up to 5 lesions covering up to 5% Body Surface Area (BSA), then 5 times per Week for 6 Weeks if tolerability permits. - Cycle 2: subjects will be treated with resiquimod gel 0.03% or resiquimod gel 0.06% for 8 Weeks: 3 times per Week for 2 Weeks, on nonconsecutive days, on up to 5% BSA, then 5 times per Week for 6 Weeks on up to 10% BSA if tolerability permits. These 2 treatment cycles of 12 Weeks each (8 Weeks treatment + 4 Weeks treatment-free) will be followed by a 12 Weeks treatment-free follow-up period. For subjects with Complete Response (CR) 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. Should subjects relapse during the follow up period; the subject will be exited from the study. Subjects will have at least 3 distinct lesions, including one 'distant' target lesion on which no treatment will be applied but which will be selected to observe a potential remote (systemic) effect. 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 the protocol.

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	The distant lesion is defined as a circumscr bed, 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, and strict avoidance of cross-contamination will be required. This distant target lesion is called 'target untreated lesion' throughout the protocol. 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. These other lesions are called treated 'non-target lesions'.
Total number of subjects (Planned):	As a screen failure rate of approximately 25 percent is anticipated, screening of approximately 112 subjects is planned in order to achieve the target of approximately 84 subjects randomized (approximately 28 per arm).
Number of clinical trial centers (Planned):	Approximately 25 centers
Region(s) / country(ies) involved (Planned):	USA, France, Germany
Clinical trial duration:	The planned clinical trial duration (from FSFV to LSLV) is approximately 32 to 34 months. The planned duration of recruitment (from FSFV to LSFV) is approximately 14 to 16 months.
Duration of subject participation:	Clinical trial participation for each subject is up to 76 Weeks, including an up to 4 Weeks screening Phase
Key Inclusion criteria	▪ ≥18 years of age at the screening visit. ▪ Have a clinical diagnosis of cutaneous T cell lymphoma (CTCL) stage IA, IB, or IIA including documentation of a skin biopsy within the last twelve (12) months with histological findings consistent with CTCL (Olsen et al, 2007). If the histological documentation is not available, a (non-target lesion) skin biopsy may be performed at the Screening visit for confirmation. ▪ For stage IIA, only subjects with a classification of N0 (No clinically abnormal peripheral lymph nodes) or N1 (clinically abnormal lymph node(s) histopathology Dutch grade 1 or NCI LN0-2) can be enrolled. ▪ Subjects must be B0 (absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL are atypical (Sezary) cells, fewer than 20% Sezary cells or fewer than 250 Sezary cells/µL. One of the following can be substituted for Sezary cells: up to 1,600/µL CD4 cells and lower than 250/µL CD4+/CD26- or CD4+/CD7- cells. ▪ Have BSA involvement corresponding to stages IA, IB or IIA CTCL with at least three distinct lesions, including one 'distant' lesion on which no treatment will be applied to observe possible systemic effect. ▪ Body Mass Index (BMI) of at least 18 kg/m^2 inclusive at the Screening visit ▪ Subjects may only be included when therapies, according to the S2k – Leitlinie – Kutane Lymphome, Stand 08/2017, are either contraindicated and/or ineffective and/or not well tolerated. (Germany only)

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Key Exclusion criteria	▪ Participation in previous studies with resiquimod gel. ▪ Known or suspected allergies or sensitivities to any component of the resiquimod gel. ▪ History of clinically meaningful allergic reactions to imiquimod. ▪ History of autoimmune disease including (but not limited to) rheumatoid arthritis, autoimmune hepatitis, autoimmune thyroiditis, Sjögren syndrome, psoriasis, or systemic lupus erythematosus. ▪ Any of the following laboratory values at Screening lab test: - Hb <10.0 g/dL for men and women - White Blood Cell (WBC) count <3000/mm^3 and/or PMN count <1500/mm^3 - Platelets <100 x 10^9/L - Creatinine clearance <50ml/min, calculated using the CKD-EPI formula - AST, ALT, ALP, or bilirubin > 1.5 ULN - INR >1.5 - Serum a bumin <3.5g/dL ▪ Any other laboratory test values at screening outside of the normal range and judged clinically significant by the investigator. ▪ Clinically significant abnormal ECG results at screening. ▪ Skin infection and/or skin ulceration at screening and baseline visit for the skin areas to be treated. ▪ Any organ transplant recipient. ▪ Any subject with a diagnosis of active malignancy or a cancer requiring treatment or expected to require treatment during the course of the trial (not including BCC, non-invasive SCC of the skin, malignant melanoma in situ, or cervical carcinoma in situ). ▪ Any uncontrolled or serious underlying disease, or any medical or surgical condition, including local or systemic disease, that may interfere with interpretation of the trial results and/or put the subject at significant risk according to investigator if he/she participates to the trial. Such diseases or conditions include (but are not limited to) severe cardiac, psychiatric, haematological and thyroid diseases or conditions. ▪ Excessive UV radiation within 1 month prior to Baseline visit or is planning intense UV exposure during the trial (e.g., subject excessively sunbathes, tanning salon use, phototherapy). ▪ Current participation in another clinical trial of a drug or device or past participation within 4 Weeks before Baseline or subject is in exclusion period from a previous clinical trial. ▪ Inability or unwillingness to undergo multiple venipunctures because of poor tolerability or poor venous access. ▪ Known sensitivity to any local anaesthetic drug ▪ Abnormal healing (hypertrophic scars, atrophic scars, dyschromic scars). ▪ History of Stage IIB or greater CTCL, or stage IIA with stage N2 (Dutch Grade 2 or NCI LN3 or greater), or with >5% circulating Sezary cells. ▪ CD8+ or large cell transformation CTCL disease. ▪ Require immediate alternative treatment for progressive CTCL. ▪ Having received at least one of the following treatment within the specified timeframes: <u>Within 12 Weeks:</u> - Total body electron beam radiation

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	Within 8 Weeks: - Imiquimod Within 4 Weeks: - Local radiation therapy - UVB therapy - PUVA - Any topical chemotherapy - Photopheresis - Systemic retinoids, systemic corticosteroids, immune response modifiers (other than imiquimod), interferon inducers - Systemic immunosuppressive drugs - Topical corticosteroids or retinoids Within 5 half-lives: - Investigational drugs or treatments - Systemic chemotherapeutic agents - Biologics (such as monoclonal antibodies) and biological immunoresponse modifiers (such as, but not limited to interferons) with immunosuppressive/immunomodulatory mechanism of action Within 2 Weeks: - Medications that are potent inhibitor and/or inducer of cytochrome P450 1A2 and 3A4 - Grapefruit juice: more than 1 glass (i.e. 240 mL) per day - At or adjacent to the target treatment lesions or on the distant untreated lesion: 1) Any surgical procedures other than biopsies related to CTCL diagnosis or follow up; 2) Any topical treatment other than bland moisturizers (creams, lotions, emollients, etc.)

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Investigational product:	
Name:	Resiquimod gel (CD11301 gel) (4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo [4,5-*c*] uinolone-1-ethanol)
Internal code:	CD11301
Pharmaceutical form:	Gel
Strength/Concentration:	0.03% and 0.06%
Dosage (total daily dose):	A thin layer (approximately 5 mg/cm^2) of resiquimod gel will be applied on 5% BSA up to a maximum of 4.25g in Cycle 1 and in Cycle 2, 5% BSA with a gradual increase to 10% BSA with a maximum dose of 8.5g.
Route:	Topical
Duration of administration:	Two cycles of eight Weeks each
Dose regimen:	▪ Cycle 1: Treatment (resiquimod gel at concentrations of 0.03% or 0.06%) will be applied on up to 5 treated target lesions covering up to 5% of BSA, in the morning, 3 times per Week (non-consecutive days) for the first 2 Weeks, then 5 times per Week for additional six Weeks if tolerability permits. After 8 Weeks Cycle 1 treatment period, subjects will have a four-Week treatment free period. ▪ Cycle 2: Each active treatment arm will continue to receive resiquimod gel at the same concentrations of 0.03% or 0.06% they were randomized to in Cycle 1. Treatment will be applied on the same treated target lesions as in Cycle 1. In addition, it may be applied on other lesions covering up to 5% of BSA (inclusive of all treated target lesions) in the morning, three times per Week (non-consecutive days) for two Weeks, then on up to 10% of BSA (inclusive of all treated target lesions) in the morning, five times per Week (consecutive or non-consecutive days) for six Weeks, if tolerability permits. Subjects will then have a four-Week treatment free washout period.
Location of treated area:	The target untreated lesion, assessed to investigate a potential remote (systemic) effect, as well as the treated target lesions must be below the neck and must not involve the genitalia, intertriginous areas, antecubital areas, or palms and soles. Treatment must not be applied to mucous membranes or to skin areas infected and/or ulcerated. Treated lesions should preferably be separate and distinct from others. The target untreated lesion will preferably be 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, and strict avoidance of cross-contamination will be required.

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Comparator product:	
Name:	CD11301 gel placebo
Internal code:	CD11301
Pharmaceutical form:	Gel
Strength/Concentration:	0%
Dosage (total daily dose):	A thin layer (approximately 5 mg/cm^2) of gel placebo will be applied on 5% BSA up to a maximum of 4.25g only in Cycle 1 and in Cycle 2 subjects will change to resiquimod gel at 0.03%. They will apply resiquimod gel 0.03% on 5% BSA with a gradual increase to 10% BSA with a maximum dose of 8.5g.
Route:	Topical
Duration of administration:	Two cycles of eight Weeks each
Dose regimen:	▪ Cycle 1: Treatment (placebo gel) will be applied on up to 5 treated target lesions covering up to 5% of BSA, in the morning, 3 times per Week (non-consecutive days) for the first 2 Weeks, then 5 times per Week for additional six Weeks if tolerability permits. After 8 Weeks Cycle 1 treatment period, subjects will have a four-Week treatment free period. ▪ Cycle 2: Subjects receiving placebo in Cycle 1 will then change to resiquimod gel 0.03% in Cycle 2. Treatment will be applied on the same treated target lesions as in Cycle 1. In addition, it may be applied on other lesions covering up to 5% of BSA (inclusive of all treated target lesions) in the morning, three times per Week (non-consecutive days) for two Weeks, then on up to 10% of BSA (inclusive of all treated target lesions) in the morning, five times per Week (consecutive or non-consecutive days) for six Weeks, if tolerability permits. Subjects will then have a four-Week treatment free washout period.
Location of treated area:	The target untreated lesion, assessed to investigate a potential remote (systemic) effect, as well as the treated target lesions must be below the neck and must not involve the genitalia, intertriginous areas, antecubital areas, or palms and soles. Treatment must not be applied to mucous membranes or to skin areas infected and/or ulcerated. Treated lesions should preferably be separate and distinct from others. The target untreated lesion will preferably be 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 and strict avoidance of cross-contamination will be required.

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Efficacy assessments: **Efficacy endpoints:**	▪ Modified Composite Assessment of Index Lesion Severity (mCAILS) (Olsen et al, 2011) ▪ Modified Severity-Weighted Assessment Tool (mSWAT) (Olsen et al, 2011) **Primary efficacy endpoint** ▪ Overall response rate (complete and partial response) of target lesions at Week 12: based upon Modified Composite Assessment of Index Lesion Severity (mCAILS) score at Week 12. Complete Response (CR) is defined as a score of '0' on the mCAILS scale. Partial response (PR) is defined as a reduction of at least 50% from Baseline, but less than 100% in the mCAILS scale **Secondary efficacy endpoints** ▪ Overall response rate (CR and PR) based upon mSWAT composite score at Week 12. CR is defined as 100% clearance of skin lesions and PR as 50 to <100% clearance from baseline without new tumors (T3) in subjects with T1, T2 or T4 only skin disease. ▪ Time to overall response (CR or PR) response based on mCAILS score. ▪ Duration of overall response (CR or PR) based on mCAILS score ▪ Time to progressive disease using mSWAT ▪ Skindex29
	CCI [redacted]
Safety assessments:	▪ Adverse Event evaluation ▪ Physical examination and body weight ▪ Vital signs (pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), temperature, and respiratory rate) ▪ Electrocardiograms ▪ Laboratory evaluations (hematology, blood chemistry, urinalysis and thyroid function tests)
Pharmacokinetic assessments:	Complete pharmacokinetic profiles of resiquimod gel and five (5) metabolites will be done for up to 36 subjects providing at Week 12, 14 and 20. For all subjects one PK sample will be collected at the time of subject visit during Week 4, 8, 12, 14, 16 and 20 visits.
Pharmacodynamic assessments:	For all subjects, blood samples will be collected for analysis of immune cell dynamics, at Baseline, Week 8, 12 and 20. For subjects providing specific consent, skin biopsies will be collected at Baseline, Week 8 and 24 in particular for

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	assessment of tumoral infiltrate and quantification of the tumoral clone representation. At selected sites and for subjects providing specific consent, additional blood samples will be collected for cellular immunology analyses at Baseline, Weeks 8, 12 and 20.
Other assessments:	▪ Skindex 29 Quality of Life Assessment Scale score (Chren et al, 1997). ▪ Patient global assessment of improvement ▪ Pruritus assessment ▪ Photography of subject BSA involvement and target lesions (treated lesions and distant lesion)
Principal statistical method:	Efficacy analysis: The primary efficacy endpoint is the Overall Response Rate (Complete or Partial Response) based on Modified Composite Assessment of Index Lesions Disease Severity (mCAILS) score at Week 12 for the target lesions. Complete Response is defined as a score of '0' on the mCAILS scale. Partial response is defined as a reduction of at least 50% from Baseline, but less than 100% in the mCAILS scale. Overall Response Rate based on mCAILS and Overall Response Rate based on mSWAT scores at Week 12 will be analyzed using the Cochran Mantel Haenszel test with the general association statistics, stratified on region (EU vs. US), if applicable. All inferential statistical tests will be two-sided and will compare each of the two active treatments to placebo, up to Week 12 (end of Cycle 1). To control the overall type I error at 5%, a Hochberg procedure will be used to compare the two doses (0.03% and 0.06%) with placebo. Treatment effect (resiquimod gel vs placebo), p-values and corresponding confidence intervals of the treatment effect (95% of CI and/or 97.5% CI depending on Hochberg procedure) will be presented for each comparison. Percent reduction in mCAILS (based on treated and untreated lesions separately) and in mSWAT will be analyzed as continuous data at Week 12 using ANCOVA and baseline corresponding mCAILS or mSWAT as covariate and treatment and region as factors. The time to overall response, the duration of response and the time to progressive disease will be summarized by treatment group using the Kaplan-Meier method. Kaplan-Meier estimates and graphs will be presented. Primary efficacy data will be summarized at Week 12 by the following subgroups if appropriate: ▪ By region (EU, USA) ▪ By stage of disease (IA vs IIA+IB) ▪ By Disease Type (mycosis fungoides, folliculotropic), if applicable ▪ By most frequently used previous therapies for CTCL (phototherapy, steroids) ▪ By age (<65 years old, ≥65 years old) ▪ By gender ▪ By race Efficacy data post Week 12 will be only descriptively summarized.

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	PK analysis (PK subjects): (1) To evaluate the treatment period effect, the following analysis will be performed separately for each treatment group if appropriate: $AUC_{0\text{-}24h}$ and C_{max} will be submitted, after logarithmic transformation (Ln), to an analysis of variance. The model will include time and subject as factors. The residual error variance will be used to compute 90% confidence intervals of the pairwise differences between time points (Week 12, Week 14 and Week 20 for $AUC_{0\text{-}24h}$ and C_{max}) on the Ln scale. The limits of the intervals will be back-transformed into exponential to obtain 90% confidence intervals of the ratios of geometric means between time points, on the original scale. (2) To evaluate the treatment effect, the following analysis will be performed separately by trial day if appropriate: $AUC_{0\text{-}24h}$, and C_{max} will be submitted after logarithmic transformation (Ln), to an analysis of variance. The model will include treatment as factor and 90% confidence intervals of the pairwise differences between treatment on the Ln scale will be calculated. The limits of the intervals will be back-transformed into exponential to obtain 90% confidence intervals of the ratios of geometric means between groups, on the original scale. Safety analysis: All safety data collected will be summarized and no inferential statistical tests are planned to be performed. Analysis: An analysis will be performed after all subjects have completed their Week 36 visit as intended in the original protocol design. Pre-identified sponsor representatives will be unblinded to data at Week 36. For the amendment 3 protocol, the study is extended to look at time to relapse on complete responders based on mSWAT from Week 36 to Week 72.
Sample size:	Sample size of this trial is based on an open-label Investigator Initiated Trial (IIT) for the treatment of early stage CTCL with resiquimod gel (Rook et al, 2015). The IIT showed approximately 58%-75% overall response rates on mCAILS for the 0.06% and/or 0.03% concentrations after one cycle (Week 12). No placebo arm was included in this trial. However, the results of a Phase 3 placebo controlled trial for Peldesine (BCX-34) cream as topical therapy for CTCL (Duvic et al, 2001 (a)) allowed to estimate the effect of a placebo. This trial appears to be well controlled, of sufficient duration (it includes 12 Weeks which is the primary time point of the present trial) and uses a similar endpoint (although not identical). The efficacy rate with placebo was approximately 20%. Based on these historical data, this Phase 2 trial is powered using the following assumptions: 60% overall response rate on mCAILS at Week 12 with resiquimod gel versus 18% with placebo. 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.

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	Assuming a discontinuation rate of 10%, approximately 84 subjects (approximately 28 subjects per treatment arm) will be randomized.

Table 1 Clinical trial schematic

Group/Number	**Group 1**	**Group 2**	**Group 3**
	n= 28	n= 28	n= 28
Cycle 1 (Baseline – Week 12)			
Treatment	Placebo gel	Resiquimod gel 0.03%	Resiquimod gel 0.06%
Treatment Frequency	3 times per Week for 2 Weeks, on non-consecutive days, on the up to 5 treated target lesions covering up to 5% BSA, then 5 times per Week for 6 Weeks if tolerability permits		
Treatment Duration	8 Weeks		
4 Weeks treatment-free between Cycle 1 and 2			
Cycle 2 (Week 12-24)			
Treatment	Resiquimod gel 0.03%	Resiquimod gel 0.03%	Resiquimod gel 0.06%
Treatment Frequency	Treatment will be applied on the same treated target lesion as in Cycle 1, 3 times per Week for 2 Weeks, on non-consecutive days, then 5 times per Week for 6 Weeks if tolerability permits. In addition, treatment may be applied on other lesions covering up to 5% of BSA (inclusive of all treated target lesions) during the first 2 Weeks, then on up to 10% of BSA (inclusive of all treated target lesions) in the following 6 Weeks, if tolerability permits.		
Treatment Duration	8 Weeks		
4 Weeks treatment-free between Cycle 2 and the follow-up period			
12-Week treatment-free follow-up period (Week 24-36)			
Treatment	No treatment of CTCL		
Duration	12 Weeks		
Assessments	Duration of responses		
36-Week treatment-free follow-up period (Week 36-72)			
Treatment	No treatment of CTCL		
Duration	36 Weeks (followed until relapse or up to Week 72)		
Assessments	Time to Relapse on mSWAT (complete responders only)		

Table 2 Schedule of assessments

Trial period		Cycle 1 <- - - - treatment period - - - -><- -no txt ->							Cycle 2 <- -treatment period- -><- no txt- ->						Follow-up Period[a]										
Visit (V)	V1	V2	V3	V4	PC[b]	V5	PC[b]	V6[c]	V7	V8	PC[b]	V9	PC[b]	V10[d]	V11	V12	V13[r]	PC[b]	PC[b]	V14	PC[b]	PC[b]	V15	PC[b]	PC[b]	V16
Week	Screening Day -28 to Day -15	Base-line Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20 (5 M)	Week 22	Week 24 6(M)	Week 28 (7M)	Week 32 (8M)	Week 36 (9M)	Week 40 (10m)	Week 44 (11m)	Week 48 (12M)	Week 52 (13M)	Week 56 (14M)	Week 60 (15M)	Week 64 16M	Week 68 17M	Week 72 18M / Early Term
Visit window (±d)			±1d	±2d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
Informed Consent/ HIPAA (US only)	X																									
Demographics	X																									
Relevant Medical History	X																									
Previous Therapies/ Procedures	X																									
Inclusion/Exclusion Criteria	X	X																								
Concomitant Therapies/ Procedures[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EFFICACY/PATIENT REPORTED OUTCOMES ASSESSMENTS																										
CTCL stage of disease	X	X						X						X			X			X			X			X
Skindex 29		X						X						X			X			X			X			X
Patient Global Assessment of Improvement								X						X			X			X			X			X
Pruritus Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
mCAILS (on the target lesions: treated and untreated)	X	X						X						X	X	X	X			X			X			X
mSWAT	X	X						X						X	X	X	X			X			X			X
Photographs	X	X						X						X			X			X			X			X

Trial period		Cycle 1 <- - - - treatment period - - - -><- no txt ->							Cycle 2 <- -treatment period- -><- no txt- ->						Follow-up Period[a]											
Visit (V)	V1	V2	V3	V4	PC[b]	V5	PC[b]	V6[c]	V7	V8	PC[b]	V9	PC[b]	V10[d]	V11	V12	V13[r]	PC[b]	PC[b]	V14	PC[b]	PC[b]	V15	PC[b]	PC[b]	V16
Week	Screening Day -28 to Day -15	Base-line Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20 (5 M)	Week 22	Week 24 6(M)	Week 28 (7M)	Week 32 (8M)	Week 36 (9M)	Week 40 (10m)	Week 44 (11m)	Week 48 (12M)	Week 52 (13M)	Week 56 (14M)	Week 60 (15M)	Week 64 16M	Week 68 17M	Week 72 18M / Early Term
Visit window (±d)			±1d	±2d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
LABORATORY/SAFETY ASSESSMENTS																										
Adverse Event[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination and Body Weight (BW)	X	X	X	X		X		X	X	X		X		X	X	X	X			X			X			X
Height	X																									
Calculate Body Mass Index (BMI) and Body Surface Area (BSA)	X																									
Vital signs (pulse rate, SBP, DBP, respiratory rate, and temperature)	X	X	X	X		X		X	X	X		X		X	X	X	X			X			X			X
ECG	X		X	X		X		X	X			X		X			X[h]									
Serial ECG												X[i]														
Urine/Serum Pregnancy Test[j]	X	X		X		X		X		X		X		X			X			X			X			X
Safety laboratory tests	X	X	X			X		X	X			X		X			X			X			X			X
Thyroid function tests	X					X						X														
PHARMACOKINETICS AND PHARMACODYNAMICS ASSESSMENTS																										
PK Assessment (full profile)[k]								X	X			X														
PK sample[l]				X		X		X[m]	X[m]	X		X[m]														
Biopsies[n]	X[q]	X				X								X												
Blood draw for immune cell dynamic analysis (PBMC)		X				X		X				X														

Trial period		Cycle 1 <- - - - treatment period - - - -><- no txt ->							Cycle 2 <- -treatment period- -><- no txt- ->						Follow-up Period[a]											
Visit (V)	V1	V2	V3	V4	PC[b]	V5	PC[b]	V6[c]	V7	V8	PC[b]	V9	PC[b]	V10[d]	V11	V12	V13[r]	PC[b]	PC[b]	V14	PC[b]	PC[b]	V15	PC[b]	PC[b]	V16
Week	Screening Day -28 to Day -15	Base-line Week 0	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20 (5 M)	Week 22	Week 24 6(M)	Week 28 (7M)	Week 32 (8M)	Week 36 (9M)	Week 40 (10m)	Week 44 (11m)	Week 48 (12M)	Week 52 (13M)	Week 56 (14M)	Week 60 (15M)	Week 64 16M	Week 68 17M	Week 72 18M / Early Term
Visit window (±d)			±1d	±2d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
At select center(s), blood draw for cellular immunology (PBMC)[o]		X		X		X		X		X		X														
OTHER																										
Trial drug(s) /supplies / diary Dispensing (D) and Accountability (A)		D	D/A	D/A		A		D	D/A	D/A		A														
Exit Form[p]																	X[s]									X[t]

a) The follow-up period (Week 24-36) is mandatory for subjects who stop treatment after Cycle 1.

b) Phone call (PC): Subject will be called by phone and asked on potential adverse events, any change in concomitant medications/procedures and pruritus assessment.

c) Week 12 visit is the last visit of Cycle 1 and the first visit of Cycle 2.

d) Week 24 visit is the last visit of Cycle 2 and the beginning of the follow-up period.

e) Should be conducted earlier if the subject discontinues before final visit.

f) Medication that continues after Screening should be recorded on the Drugs/Therapies form of the eCRF. Medical or surgical procedures occurring after Screening should be recorded on the Medical and Surgical Procedures form of the eCRF.

g) Adverse Events have to be collected starting from the time of Informed Consent signature onwards. Abnormal laboratory values from the screening visit are to be recorded as Medical History. Events related to trial procedures (i e., fainting due to venipuncture) that occur prior to first dose of trial drug are to be recorded as Adverse Events.

h) If the ECG is abnormal at Week 24, it will be repeated at Week 36.

i) Serial ECGs will be done for the PK subjects with full PK assessments only (up to 36). ECG will be performed at the ime of the trial drug application (T0) and 2, 4, 6, 8, 12, 24 hours after the trial drug application.

j) Only for females of childbearing potential; serum test at Screening, then urine test (or serum) at Baseline and following monthly visits; UPT or serum must have a sensitivity threshold of 25 mIU/mL or less for human chorionic gonadotropin (hCG).

k) PK full profiles to be collected from up to 36 subjects. Those days, product application will be done on site. See Table 3 for imepoints.

l) One PK sample for proof of exposure, to be collected for all subjects at the time of site visit (date/time of last trial product application to be recorded in the eCRF).

m) Only for non PK subjects.
n) Optional: only for subjects providing specific consent, and at select sites. See Table 4 for details on biopsies.
o) Optional: only for subjects providing specific consent, and at select sites.
p) Exit form should be signed after subject data collection has been completed.
q) Biopsy for CTCL confirmation if none is available within the last 12 months (non-target lesion).
r) Subjects with Complete Response as determined by the Investigator from the mSWAT Skin Involvement assessment at Week 36 will be followed for an additional 36 Weeks.
s) Subjects not a complete responder of mSWAT will be exited the study at Week 36.
t) Subjects who are complete responders of mSWAT at Week 36, will be followed until relapse or Week 72 then the Exit Form will be completed. Relapse is any disease recurrence in those with complete response based upon baseline mSWAT

.

All subjects will undergo PK measures for proof of exposure as indicated in the schedule of assessments (see Table 2).

A subset of up to 36 subjects will undergo a full PK sampling at the following timepoints:

Table 3 Pharmacokinetic assessment timespoints (full PK profile)

Visit	Week 12[a]	Week 14[a]	Week 20[a]
Complete PK profile (for up to 36 PK subjects)[b]	Pre-dose, 2, 4, 6 ,8, 12, 24 and 48 hours	Pre-dose, 2, 4, 6, 8, 12 and 24 hours	Pre-dose, 2, 4, 6, 8, 12, 24, 48 and 72 hours

a) Application of trial product will be done on site for the subset of PK subjects
b) Subjects with specific consent

Table 4 Pharmacodynamic assessment timepoints

Cycle 1 (% 5 BSA)			
Visit	**Week 0, First application[a]**	**Week 4**	**Week 8**
4-mm biopsies[b] or 6-mm biopsies[d]	On a target treated lesion (x1) + on a non-lesional area (x1) + on the untreated target lesion (x1)	-	On the same treated target lesion (x1)
Immune cell dynamics	Pre-dose	-	One sample collected at time of subject visit
Cellular immunology[c]	Pre-dose	One sample collected at time of subject visit	One sample collected at time of subject visit

Cycle 2 (up to 10% BSA)				
Visit	**Week 12[a]**	**Week 16**	**Week 20**	**Week 24**
4-mm biopsies[b] or 6-mm biopsies[d]		-	-	On the same treated target lesion (x1) + on the untreated target lesion (x1)[e]
Immune cell dynamics	Pre-dose	-	One sample collected at time of subject visit	-
Cellular immunology[c]	Pre-dose	One sample collected at time of subject visit	One sample collected at time of subject visit	

a) Application done on site.
b) Biopsies are optional for subject providing specific consent and should be taken before trial drug application.
c) At select center(s) only.
d) At select centers only, optional for subjects providing specific consent.
e) If at least 50% regression is observed.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	*Term*
°C	Degrees Celsius
°F	Degrees Fahrenheit
AE	Adverse Event
ALP	Alkaline Phosphatase
ANCOVA	Analysis of covariance
approx	Approximately (or use ‘about’, not C. or ca.)
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the Curve
BCC	Basal Cell Carcinoma
BLQ	Below the Limit of Quantitation
BMI	Body Mass Index
BSA	Body Surface Area
BP	Blood Pressure
BW	Body Weight
mCAILS	Modified Composite Assessment of Index Lesion Severity
CDMS	Clinical Data Management System
CI	Confidence Interval
Cmax	Maximum Concentration
CR	Complete Response
CRA	Clinical Research Associate

Abbreviation	*Term*
CRF	Case Report Forms
CRO	Contract Research Organization
CSO	Clinical Safety Officer
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-Cell Lymphoma
CyTOF	Mass cytometry
d	Day
DBP	Diastolic Blood Pressure
DC	Dendritic cells
DMP	Data Management Plan
eCRF	electronic Case Report Forms
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
ECG	Electrocardiogram
EMA	European Medicines Agency
ET	Early Termination Visit
etc	Et cetera
EU	European Union
FDA	Food and Drug Administration
FSFV	First Subject First Visit (date of first subject included i.e., informed consent signature)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation	*Term*
Hb	Hemoglobin
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICDRG	International Contact Dermatitis Research Group
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
i.e.	That is (Latin: id est)
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IIT	Investigator Initiated Trial
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IU	International Units
IUD	Intrauterine Device
LC/MS-MS	Liquid chromatography tandem-mass spectrometry
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantitation
LSFV	Last Subject First Visit (date of last subject included i.e., informed consent signature)

Abbreviation	*Term*
LSLV	Last Subject Last Visit (date of last subject's last trial visit)
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
mL	Milliliter
mSWAT	Modified Severity-Weighted Assessment Tool
N/A	Not Applicable
NK cells	Natural Killer cells
OTC	Over-the-Counter
PBMC	Peripheral Blood Mononuclear Cells
PC	Phone Call
PD	Pharmacodynamics
PE	Physical Examination
PK	Pharmacokinetics
PMN	Polymorphonuclear cells
PP	Per-Protocol
PR	Partial Response
PUVA	Psoralen and ultraviolet A
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCC	Squamous Cell Carcinoma
SD	Standard Deviation

Abbreviation	*Term*
SIN	Subject Identification Number
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Sezary Syndrome
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	Half-life
TLR	Toll-like Receptor
TMF	Trial Master File
tmax	Time to Maximum Concentration
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
UV	ultraviolet
V	Visit
WBC	White Blood Cell

1 BACKGROUND AND RATIONALE

1.1 Medical background and Short rationale for the clinical trial

Primary cutaneous T-cell lymphoma (CTCL), whose most common forms are mycosis fungoides (MF) and Sezary syndrome (SS), is a cancer of the immune system. Lymphomas are generally classified into Hodgkin's and non-Hodgkin's lymphomas, the latter group a heterogeneous group of cancers to which CTCL belongs.

CTCL is T-cell related. The malignant T-cells migrate to the skin, resulting in characteristic skin lesions and symptomatology.

CTCL is a rare disease. The incidences of the disease are comparable in Europe and USA. For example, CTCL affects fewer than 200,000 people in the United States. The total number of cases of CTCL registered in the US from 1973 – 2009 was 6230 with an annual age-adjusted incidence rate of 7.5 cases per million persons. While previously thought to be on the rise, the incidence rate now appears to be stable (Eder et al, 2015) (Korgavkar et al, 2013).

MF is the most common form of this disease and has an indolent course. Diagnosis is generally confirmed through biopsy as the disease can resemble eczema (Eder et al, 2015) (Koh et al, 1995).

Prognosis in early stage CTCL can be quite good with expected 5-year survival rates ranging from over 96% for stage IA to 49-73% for stage IIA. Topical and systemic treatments are numerous (Whittaker et al, 2003) (Zackheim et al, 1999).

Treatment depends upon the stage of the disease as well as patient factors, and early stages may respond to a variety of topical treatments such as psoralen ultraviolet A (PUVA), retinoids, electron beam radiation, steroids, and topical chemotherapy such as nitrogen mustard (Zelenetz et al, 2014). The goal of early treatment is to clear lesions and maintain such clearance or stable disease as long as possible until relapse and/or disease stage progression (Jawed et al, 2014). No treatment, topical or systemic, has been unequivocally shown to be curative, in particular at the early stages of the disease when patients experience recurrent relapses.

One new potential method of treatment is via innate immune system activation. The imidazoquinolines are a class of small organic molecules that can activate antigen presenting cells such as dendritic cells, macrophages, B-lymphocytes and monocytes. These immune response modulators act via the stimulation of specific Toll-like receptors (TLRs), to induce the production of several cytokines including interleukin 12 and interferon alpha, which ultimately leads to the set-up of adaptive immune responses. Examples of these drugs include resiquimod and imiquimod (Woodmansee et al, 2006).

Imiquimod is an immune response modifier that acts through TLR 7. It has been approved to treat actinic keratosis and has been used off-label to treat different forms of skin cancer, including CTCL (Poligone et al, 2010). It directly and indirectly results in the stimulation of production of interferon alpha and gamma, as well as interleukins 1, 6, 8, 10 and 12 (Martinez-Gonzalez et al, 2008). It has

indirect anti-tumor and anti-viral effects via the same immune mechanisms as resiquimod. It has been shown to be effective and safe in the treatment of early stages of CTCL including the MF subtype and is included in the National Comprehensive Cancer Network (NCCN) treatment guidelines as an option for the treatment of CTCL (Zelenetz et al, 2014). Resiquimod has been shown to be more potent at inducing cytokine secretion (Gibson et al, 2002).

1.2 Drug profile

Resiquimod belongs to the imidazoquinolines class and hence acts upon the cells of the innate immune system to augment the release and production of cytokines.

The main mechanism of function is through the activation of toll-like receptors (TLRs) 7 and 8. TLRs recognize molecular patterns encoded by microorganisms, and such recognition is important in the activation of the innate immune system and the elimination of foreign pathogens. Resiquimod stimulates this activation (Woodmansee et al, 2006).

Resiquimod has been shown to indirectly stimulate the adaptive immune system by promoting interferon gamma production via T-lymphocytes and Natural Killer cells (Brugnolo et al, 2003).

Through enhancing antigen presentation by innate immune cells and T-Helper cell cytokines including interleukin 12 and interferon alpha directly and interferon gamma indirectly, the drug influences cell-mediated immunity.

Resiquimod has been investigated previously in the treatment of actinic keratoses, basal cell carcinoma, common warts, melanoma, herpes simplex (genitalis and labialis), hepatitis C and CTCL. As a result of the mechanism of action of the drug, it induces local activation of innate immunity as well as production of cytokines such as interferons alpha and gamma, associated with antiviral and anti-tumor effects (Meyer et al, 2013).

As of March 2017, 41 clinical trials have been conducted by previous Sponsors. A total of 3548 subjects were included in these trials; of them, 2500 subjects were exposed to various formulations and concentrations of resiquimod.

One additional clinical trial has been initiated recently by Galderma with resiquimod gel (phototoxicity study in healthy volunteers, RD.06.SPR.106984). Thirty-five (35) 24 out of 35 planned subjects had been enrolled in the USA.

Lastly, an Investigator Initiated Trial (IIT) was conducted in 12 subjects with early stage CTCL using resiquimod gel (Rook et al, 2015). Subjects involved in the aforementioned trials were exposed to daily doses up to 2.5 mg of resiquimod (active substance) per application, at concentrations ranging from 0.01% to 0.25%.

Resiquimod absorption, distribution, metabolism and excretion have been fully characterized using the oral route. Once absorbed, resiquimod is extensively metabolized via aromatic hydroxylation and O-dealkylation followed by conjugation.

A comprehensive metabolism profiling of resiquimod was performed throughout three *in vitro* metabolism studies and one in vivo human AME trial using oral [^{14}C]-resiquimod, i.e. studies R-848-DM-21, R-848-DM-37, R-848-DM-40, and 1416-RESI respectively. These studies demonstrated that:

- CYP1A2 is the primarily isoenzyme responsible for the production of 6-OH-resiquimod (S-32899), the major metabolite detected in vivo, and also contributes to the production of 7-OH-resiquimod (S-32483);
- The formation of the desethyl metabolite (S-28371), the second most common in vivo human metabolite (as glucuro-conjugated form) is mediated primarily by CYP3A4;
- CYP3A4 contributes to the formation of the N-oxide metabolite (S-32544). This metabolite was mainly detected in vitro using human material and was present at low level in serum samples;
- CYP 1A2 and CYP 3A4 contribute to the formation of 8-OH-resiquimod (S-31451).

Overall, results demonstrated that resiquimod was extensively metabolized in vitro and a total of 5 Phase I metabolites were identified in serum (hereafter S-28371, S-31451, S-32483, S-32899 and S-32544)

After administration of a radioactive dose of resiquimod by the oral route to 6 healthy volunteers, approximately 71% and 25% of the dose, was recovered in urine and feces, respectively. Scant amounts of resiquimod were excreted unchanged in either urine (<5%) or feces (<1%), indicating resiquimod is well absorbed after oral dosing and primarily cleared via metabolism (trial 1416-RESI).

Two (2) Phase 1 studies provide single dose and multiple-dose pharmacokinetics data by oral route up to 0.03 mg/kg (studies 1210-R848 and 1248-R848). By the oral route, resiquimod C_{max} and AUC concentrations increased in a dose proportional manner and no accumulation of resiquimod or its metabolite was observed with twice-Weekly dosing. A mean $AUC_{0\text{-}24\ h}$ of 27.7±8.9 ng.h/mL was obtained from healthy volunteers receiving an oral dose of 0.03 mg/kg, 2 times a Week for 5 Weeks (trial 1248-R848).

Two Phase 1 studies provide single dose and multiple-dose pharmacokinetic data by topical route up to 0.03 mg/kg (studies 1218-R848 and 1246-R848). By the topical route, resiquimod was investigated in healthy volunteers, where, the resiquimod gel (0.01 to 0.25%) was applied over a 50 cm^2 area of the upper arm twice a Week for 8 or 24 hours per application for up to 3 Weeks duration. After single or repeated topical administrations, none of the subjects in any of the groups had quantifiable resiquimod serum concentrations (≤10 to 20 pg/mL), with the exception of the last dose samples for one subject who received the highest resiquimod dose in trial 1246-R848. In that trial, utilizing (1) the highest topical mg/kg dose and (2) the highest formulation strength tested to date (0.04 mg/kg and 0.25% gel concentration strength, respectively), a subject had resiquimod concentrations of 134, 230 and 152 pg/mL at pre-dose and at 8 and 12 hours post-dose, respectively. Based on these 3 concentrations, the $AUC_{0\text{-}24\ h}$ was extrapolated to 3.2 ng.h/mL for topical dose of 0.04 mg/kg.

Adverse effects of resiquimod gel include application site reactions (such as erythema, edema and erosions) that are essentially dose dependent and self-limiting, depending upon dosage frequency, duration of dosing, concentration of drug and integrity of the skin at the application site. These application site reactions are consistent with the predicted pharmacologic effects resulting from localized immune stimulation. In the present trial, the trial drug should not be applied on skin areas with infection and/or ulceration.

Systemic effects include transient decreases in neutrophils, possibly as a result of cellular trafficking in response to locally induced cytokines. An influenza-like syndrome has been observed with increasing exposure to the drug, thought to be related to interferon production and consistent with the anticipated consequences of TLR activation. Given that the drug primarily acts via a Th-1 immune response, conditions associated with a predominance of this form of immunity, such as psoriasis, should be carefully monitored. Moreover as resiquimod activates mDC through TLR8 engagement, subjects with a history of, or current, autoimmune disease (especially systemic lupus erythematosus or Sjögren syndrome) or organ transplant (that are under immunosuppresive treatment) are not eligible for the trial.

In animal reproductive and developmental toxicology studies with resiquimod via oral delivery, embryo- and feto-toxicity at maternally toxic doses were observed. As a cautionary measure, women of childbearing potential will be required to use an acceptable method of contraception to be eligible for the planned clinical trial.

The immune–modulating effects of resiquimod suggest it has a role in a variety of skin lesions and conditions. Topical resiquimod may be an alternative to topical chemotherapy aiming at inducing anti-tumoral immune response and at eradicating immunosuppressive environment induced by the tumoral cells, such as malignant lymphocytes in CTCL.

In an open-label, Phase I, investigator-initiated trial (IIT) using resiquimod gel, twelve subjects with stage IA, IB and IIA CTCL were treated (Rook et al, 2015). Subjects were treated for an eight Week active treatment period with varying frequencies per Week from once to a maximum of seven times, changing at two-Week intervals and subject to tolerability. Dose concentrations used were 0.03% and 0.06%. A daily dose of 0.5g of resiquimod gel was applied on up to 100cm^2 of body surface area (BSA) per treatment. Between these 8-Week active treatment cycles, subjects had a four-Week hiatus to allow the skin to recover such that it could be properly assessed for treatment effect.

Subjects had previously failed on average 6 previous treatments, yet favorable responses were obtained using common composite efficacy measures, such as the Severity Weighted Assessment Tool (SWAT) analysis. Positive effects on distant non-treated lesions were also observed and postulated to be mediated by systemic effect of the drug. The data might suggest the existence of a remote effect of resiquimod gel for the treatment of CTCL. Further assessment is needed in the present Phase 2 trial to substantiate the observation. The safety profile of resiquimod gel in the IIT was acceptable, with primarily topical irritation-related adverse events being noted. Four subjects experienced a total of 5 adverse events of low-grade fever; three of these adverse events were

assessed as drug-related. Tolerance was noted over time (i.e. in Cycle 2 compared to Cycle 1) for both local reactions and systemic adverse effects such as flu-like syndrome.

No Serious Adverse Event was reported in the trial and no subject discontinued due to a drug-related adverse event.

Rationale for the present Phase 2 trial is based on the results of this recent 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. This trial is designed to compare the treatment effect of two concentrations of resiquimod gel (0.03% and 0.06%) as well as to establish the complete pharmacokinetic profile in terms of single and repeated dosing in this patient population.

Both quantification of effect versus placebo as well as the reproducibility of the efficacy observed in the IIT trial will be evaluated. While the drug has been used in significant numbers of subjects both in pharmacokinetic studies as well as studies examining effectiveness in various disease states, overall exposure to resiquimod gel has been limited either by concentration of drug, duration of use, or BSA treated, or a combination of all three elements. This trial design is intended to determine an optimal dose and regimen while maintaining acceptable tolerability and systemic safety profile. Adverse events will be recorded at all trial visits to better characterize the safety profile of the drug in terms of both local and systemic adverse effects. The safety profile, final treatment regimen and concentration will inform subsequent Phase 3 trial design.

1.3 Risk/Benefit assessment

The highest resiquimod gel exposure measured in one healthy volunteer after topical dosing was recorded in trial 1246-R848 after three Weeks treatment (2 times per Week) (see Investigator's Brochure). One subject had resiquimod concentrations of 134 pg/mL at pre-dose and 230 and 152 pg/mL at 8 and 12 hours post-dose, respectively, and the $AUC_{0\text{-}24h}$ was extrapolated to 3.2 ng.h/mL for topical dose of 0.04 mg/kg (0.25% gel concentration applied on 50 cm^2).

This most exposed subject, receiving a topical dose of 0.04 mg/kg. This subject presented with an $AUC_{0\text{-}24h}$ 9-fold lower than the exposure obtained with an oral dose of 0.03 mg/kg (27.7±8.9 ng.h/mL).

This oral dose was considered as acceptably tolerated, despite expected systemic pharmacologic effects (Trial 1248-R848) (See Table 5). Indeed, at this level of systemic exposure ($AUC_{0\text{-}24h}$: 27.7 ng.h/mL) adverse events were associated with the pharmacological effects of the drug, i.e. local site reactions and systemic effects of flu-like syndrome. Therefore, the oral dose of 0.03 mg/kg was considered as acceptably tolerated. It is anticipated that, with the maximized clinical scenario (i.e. maximum treated surface of 10% BSA and highest dose of 0.06%), the AUC will be lower than in Trial 1248-R848. In the present Phase 2 trial, the estimated AUC ratio for the highest dose of 0.06% is 8 in Cycle 1 and 4 in Cycle 2.

In this proposed Phase 2 trial, a thin layer of resiquimod gel (0.03 % or 0.06 %) will be applied on target lesion up to 5 % BSA in Cycle 1. A maximal applied dose of 4.25 g of Gel was fixed based on the assumption that approximately 5 mg/cm^2 will be applied on 5% BSA (850 cm^2 for a 70 kg/ bw subject with a total BSA: 1.7 m^2). This maximal applied dose of gel will lead to a maximal resiquimod dose of 2.55 mg for the highest tested strength in Cycle 1 (0.06 %). When normalized to body weight (70 kg), the highest applied dose in Cycle 1 will be the same as the dose previously tested in healthy volunteer (i.e. 0.04 mg/kg). It is planned to gradually increase the daily topical applied dose from 0.04 mg/kg in Cycle 1 to 0.09 mg/kg for Cycle 2. Furthermore, complete PK profile will be collected on a subset of subjects (up to 36) in order to capture the total daily systemic exposure to resiquimod and the five potential Phase 1 metabolites in the target patient population in each cycle.

Table 5 Estimated safety ratios between systemic exposure after oral and topical administration in human

	Trial 1248-R848 multiple dose by oral route	Trial 1246-R848 multiple dose by topical route	Estimated human exposure with 5% BSA in the current trial	Estimated human exposure with 10% BSA in the current trial
Dose AUC_{0-24h} (ng.h/mL)	0.03mg/kg 27.7	0.04mg/kg 3.2	0.0425mg/kg 3.4[a]	0.085mg/kg 6.8[a]
AUC_{0-24h} Ratio (Oral/Topical)	-	9	8	4

a-with 5mg/cm^2 of the highest (0.06%) concentration

The two concentrations (0.03% and 0.06%) of resiquimod gel to be evaluated in this Phase 2 trial are the same as those assessed in the IIT (Rook et al, 2015). These concentrations have been shown to provide good efficacy results and had an acceptable tolerability and systemic safety profile in the IIT.

There is a need to characterize an optimal dose regimen. It is planned to apply the trial drug 3 times per Week (non-consecutive days) for the first two Weeks of each treatment cycle, then 5 times per Week (consecutive or non-consecutive days) for the following six Weeks. The trial drug will be applied on up to 5% BSA in Cycle 1 and up to 10% BSA in Cycle 2, considering tolerance which was noted over time in the IIT.

For the sake of risk minimization, rules for dose adjustment and/or for trial discontinuation have been defined (see Section 6.4) at the subject level, based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. An Independent Data Monitoring Committee (IDMC) will be set-up for the trial and will review safety data on an ongoing basis.

Safety monitoring will both characterize the tolerability profile of the dosing regimen, as well as explore possible safety signals. The extent and severity of all systemic events will be assessed, particularly in terms of changes in haematological parameters, and their significance, if any.

In animal reproductive and developmental toxicology studies conducted with resiquimod via oral route, embryo and fetotoxicity were observed only at maternally toxic doses. Women of childbearing potential (WOCBP) can be included in the study provided they have negative pregnancy tests at Screening (serum test) and Baseline (urine test, UPT), and they agree to use an acceptable method of contraception throughout the trial and for at least 1 month after the last trial drug application. Monthly UPTs (or serum) will be done throughout the study and, if a pregnancy occurs during the study, the study drug will be immediately discontinued and the subject will be withdrawn from the study.

With regular monitoring of efficacy and safety, the trial design will assist in determination of an optimal treatment duration, dose frequency, and drug concentration that will be both efficacious and have an adequate safety and tolerability profile. The trial will also assess the possibility of a systemic effect of resiquimod gel on non-treated distant lesions.

The use of placebo in the first cycle of the trial is considered acceptable, because of the long and protracted course of early stage CTCL with a relatively good prognosis and survival rate (Koh et al, 1995) (Whittaker et al, 2003) (Zackheim et al, 1999). Furthermore, during the second part of the trial, all subjects will receive investigational treatment.

2 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 Clinical trial 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% BSA in subjects with early stage CTCL.
- To assess a systemic effect of resiquimod gel on lesions distant from the treatment area(s).

2.2 Clinical hypothesis

The clinical hypothesis is that resiquimod gel (0.03% and 0.06%) will provide a better efficacy than corresponding placebo with an acceptable safety profile. This efficacy hypothesis of this trial is based on an open-label Investigator Initiated Trial (IIT) for the treatment of early stage CTCL with resiquimod gel (Rook et al, 2015). The IIT showed approximately 58%-75% overall response rates evaluated using Modified Composite Assessment of Index Lesion Severity (mCAILS) after one cycle (Week 12) for resiquimod 0.06% and/or 0.03% concentrations. This trial did not include a placebo arm. However, the results of a Phase 3 placebo controlled trial for Peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma (Duvic et al, 2001 (a)) allowed to estimate

the effect of a placebo. This trial appears to be well controlled, of sufficient duration (it includes 12 Weeks which is the primary time point of the present trial) and uses a similar endpoint (although not identical). The efficacy rate with placebo was approximately 20%.

Based on these historical data, this Phase 2 trial is powered using the following assumptions: 60% overall response rate on mCAILS at Week 12 with resiquimod gel versus 18% with placebo.

An additional hypothesis is that the two regions (US and Europe) are consistent regarding efficacy.

3 OVERALL CLINICAL TRIAL DESCRIPTION

3.1 Trial design

This is a randomized, double blind, multi-centre, placebo-controlled, three-arm parallel-group, trial in approx. 84 subjects with early stage CTCL. Subjects will be stratified by stage of disease, to ensure there are comparable numbers of subjects in stage IA and in stage (IB+IIA) in each of the active treatment arms and placebo arm of the trial. Stratification will also be attempted by region if possible (EU vs USA).

The following treatments will be evaluated:

- Resiquimod gel 0.03% (n=28)
- Resiquimod gel 0.06% gel (n=28)
- Placebo gel (n=28) (only during Cycle 1 then resiquimod gel 0.03% in 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 Week 12, 14 and 20.

Subjects will undergo one treatment ‘cycle’ with eight Weeks on treatment followed by 4 Weeks without treatment (Cycle 1). The treatment will commence with application 3 times per Week (on non-consecutive days) for two Weeks before increasing to 5 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 Section 6.4). Treated area will be maximum 5% body surface area (BSA) as estimated via Lund-Browder chart in this first cycle (Wachtel et al, 2000).

At Week 12, the active treatment arms will continue with an additional treatment ‘cycle’ (Cycle 2) similar to the first one (8 Weeks with treatment + 4 Weeks without treatment), with subjects allocated to receive placebo in the first cycle switched to receive active treatment with resiquimod gel 0.03% for their second treatment cycle. For each treatment arm, treated area will be maximum 5% BSA for the first two Weeks, then up to 10% BSA for the remaining 6 Weeks of treatment in the second cycle.

To be included in the trial, subjects will have at least 3 distinct lesions, including one ‘distant’ lesion on which no treatment will be applied but which will be selected to observe a potential remote (systemic) effect. 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 the protocol. The distant 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, and strict avoidance of cross-contamination will be required. This distant lesion is called 'target untreated lesion' throughout the protocol. 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, as defined below (see section 5.3.3 and Appendix 2), will result in discontinuation of the trial for the subject.

In the event a lesion resolves within the first 8 Weeks of treatment, treatment should continue to until the end of Cycle 1.

In case a lesion is cleared (complete response according to 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 (as defined in Appendix 2) 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 Investigator from the mSWAT Skin Involvement assessment at Week 36, will be followed to Week 72 or until relapse to assess time to relapse.

3.2 Independent data monitoring committee (IDMC)

An IDMC will be set-up to monitor safety data generated in this clinical trial and make appropriate recommendations to the Sponsor. The members of the IDMC will not include any sponsor representative or any investigator of the trial. The IDMC will supervise the subjects' safety as defined in the IDMC charter. The IDMC will inform the Sponsor and suggest actions to be taken, if safety signals are observed.

The specific roles of the IDMC include, but are not limited to:

- Meet periodically to review individual data and summary analyses,
- Monitor evidence for treatment harm with respect to systemic and local safety
- Assess data quality, including completeness,
- Suggest additional data analyses,
- Maintain and document any decisions and activities taken during IDMC meetings,

Further details regarding the IDMC's role and activities will be outlined in a separate IDMC charter document.

4 CLINICAL TRIAL DURATION AND TERMINATION

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. An analysis will be performed and a clinical study report will be written after all subjects have completed their Week 36 visit as intended in the original protocol design. The protocol amendment 3, extends the study to measure time to relapse on complete responders from Week 36 to Week 72. An addendum to the clinical study report will be written after all subjects in the extension period are complete.

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 76 Weeks, including an up to 4 Weeks screening Phase.

The Sponsor may decide to prematurely terminate or suspend the participation of a particular clinical trial center (for example, for lack of subject enrollment or non-compliance with clinical trial protocol, regulation, or GCP) or prematurely suspend the clinical trial (for example, for safety, trial drug(s) quality, regulatory, efficacy, or logistical reasons) at any time with appropriate notification.

5 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

5.1 Number of subjects

As a screen failure rate of approximately 25 percent is anticipated, approximately 112 subjects will be screened in order to get approximately 84 subjects enrolled (approximately 28 per arm).

5.2 Recruitment Procedure

Subjects may be recruited from the community or through the investigator's known database of patients. Recruitment of subject with advertising including any printed materials, audio or visual records, will require approval by the IRB/IEC prior to use.

5.3 Clinical trial population characteristics

In order to be eligible for the clinical trial, subjects must fulfill all of the following criteria (when applicable). These criteria are applicable at both screening and baseline unless specified. Should a subject screen fail, they may only be re-screened once.

5.3.1 Inclusion criteria

1. Adults ≥18 years of age at the screening visit.
2. Have a clinical diagnosis of cutaneous T cell lymphoma (CTCL) stage IA, IB, or IIA including documentation of a skin biopsy within the last twelve (12) months with histological findings consistent with CTCL (Olsen et al, 2007). If the histological documentation is not available, a (non-target lesion) skin biopsy may be performed at the Screening visit for confirmation.
3. For stage IIA, only subjects with a classification of N0 (No clinically abnormal peripheral lymph nodes) or N1 (clinically abnormal lymph node(s) histopathology Dutch grade 1 or NCI LN0-2) can be enrolled.
4. Subjects must be B0 (absence of significant blood involvement: ≤5% of peripheral blood lymphocytes or <250/mcL are atypical (Sezary) cells, fewer than 20% Sezary cells or fewer than 250 Sezary cells/µL. One of the following can be substituted for Sezary cells: up to 1,600/µL CD4 cells and lower than 250/µL CD4+/CD26- or CD4+/CD7- cells.
5. Have BSA involvement corresponding to stages IA, IB or IIA CTCL with at least three distinct lesions, including one 'distant' lesion on which no treatment will be applied to observe possible systemic effect.
   Note: Distant lesion is defined as a circumscribed, discrete lesion that will not 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, and strict avoidance of cross-contamination will be required.
   Eligible lesions to treatment must be below the neck and must not involve the genitalia, intertriginous areas, antecubital areas, palms of the hands or soles of the feet, or occur on ulcerated or infected skin. However, the presence of such lesions is not an exclusion criterion to enter the trial. Mucous membranes are not to be treated. Target lesions for mCAILS assessment are to be selected upon the basis of being most representative of the subject's stage of disease.
6. Woman of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy)
7. Woman of childbearing potential: an acceptable method of contraception must be used during the trial and at least 1 month after the last trial drug application and must be combined with a negative serum pregnancy test obtained during screening visit and a negative urine pregnancy test (UPT) obtained during baseline visit (the baseline visit must be performed at least 15 days after the Screening visit).

   For purposes of this trial, the Sponsor defines "acceptable methods of contraception" as:

   a) Oral birth control pills administered for at least 1 monthly cycle prior to administration of the trial drug.

b) A synthetic progestin implanted rod (eg, Implanon®) for at least 1 monthly cycle prior to the trial drug administration but not beyond the 4th successive year following insertion

c) Intrauterine devices (IUDs), inserted by a qualified clinician for at least 1 monthly cycle prior to trial drug administration.

d) Medroxyprogesterone acetate (eg, Depo-Provera®) administered for a minimum of 1 monthly cycle prior to administration of the trial drug and continuing through 1 month following trial completion.

e) True abstinence, if in line with the preferred and usual lifestyle of the subject.

f) Double barrier method: a combination of male condom with either cap, diaphragm, or sponge with spermicide.

8. Body Mass Index (BMI) of at least 18 kg/m2 inclusive at the Screening visit
9. Understand and sign an Informed Consent Form at the screening visit, prior to any investigational procedure being performed.
10. Willing and able to adhere to the protocol requirements, including but not limited to trial drug dosing, trial visits, medication and treatment restrictions, and laboratory and other pharmacokinetic and safety assessments.
11. Willing and able to discontinue concomitant medications or treatments for CTCL during the trial.
12. Willing to abstain from therapeutic sunbathing, tanning beds, and other such equipment that provide a confounding UV light source for the duration of the trial.
13. According to country regulation, subjects should be affiliated with a National Health System at screening visit.
14. Apprised of HIPAA (applicable to subjects in the US), and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit.
15. Subjects may only be included when therapies, according to the S2k – Leitlinie – Kutane Lymphome, Stand 08/2017, are either contraindicated and/or ineffective and/or not well tolerated. (Germany only)

5.3.2 Exclusion criteria

1. Participation in previous studies with resiquimod.
2. Known or suspected allergies or sensitivities to any component of the resiquimod gel.
3. History of clinically meaningful allergic reactions to imiquimod.
4. History of autoimmune disease including (but not limited to) rheumatoid arthritis, autoimmune hepatitis, autoimmune thyroiditis, Sjögren syndrome, psoriasis, or systemic lupus erythematosus.

5. History of drug and/or alcohol abuse within the previous 12 months before baseline.
6. Pregnant or lactating woman or woman who intends to conceive a child during the clinical trial or within 1 month after the last trial drug application.
7. Any of the following laboratory values at Screening lab test:
    - Hb <10.0 g/dL for men and women
    - White Blood Cell (WBC) count <3000/mm^3 and/or PMN count <1500/mm^3
    - Platelets <100 x 10^9/L
    - Creatinine clearance <50ml/min, calculated using the CKD-EPI formula
    - AST, ALT, ALP, or bilirubin > 1.5 ULN
    - INR >1.5
    - Serum albumin <3.5g/dL
8. Any other laboratory test values at screening outside of the normal range and judged clinically significant by the investigator.
9. Clinically significant abnormal ECG results at screening.
10. Skin infection and/or skin ulceration at screening and baseline visit for the skin areas to be treated.
11. Any organ transplant recipient.
12. Any subject with a diagnosis of active malignancy or a cancer requiring treatment or expected to require treatment during the course of the trial (not including BCC, non-invasive SCC of the skin, malignant melanoma in situ, or cervical carcinoma in situ).
13. Any uncontrolled or serious underlying disease, or any medical or surgical condition, including local or systemic disease, that may interfere with interpretation of the trial results and/or put the subject at significant risk according to investigator if he/she participates to the trial. Such diseases or conditions include (but are not limited to) severe cardiac, psychiatric, haematological and thyroid diseases or conditions.
14. Excessive UV radiation within 1 month prior to Baseline visit or is planning intense UV exposure during the trial (e.g., subject excessively sunbathes, tanning salon use, phototherapy).
15. Current participation in another clinical trial of a drug or device or past participation within 4 Weeks before Baseline or subject is in exclusion period from a previous clinical trial.
16. Inability or unwillingness to undergo multiple venipunctures because of poor tolerability or poor venous access.
17. Known sensitivity to any local anaesthetic drug
18. Abnormal healing (hypertrophic scars, atrophic scars, dyschromic scars).

19. History of Stage IIB or greater CTCL, or stage IIA with stage N2 (Dutch Grade 2 or NCI LN3 or greater), or with >5% circulating Sezary cells.
20. CD8+ or large cell transformation CTCL disease.
21. Require immediate alternative treatment for progressive CTCL.
22. Having received at least one of the following treatment within the specified timeframes:

Treatment	Timeframe of treatment initiation (Day 0)
Total body electron beam radiation	Within 12 Weeks
Imiquimod	Within 8 Weeks
Local radiation therapy	Within 4 Weeks
UVB therapy	Within 4 Weeks
PUVA	Within 4 Weeks
Any topical chemotherapy	Within 4 Weeks
Photopheresis	Within 4 Weeks
Systemic retinoids, systemic corticosteroids, immune response modifiers (other than imiquimod), interferon inducers	Within 4 Weeks
Systemic immunosuppressive drugs	Within 4 Weeks
Topical corticosteroids or retinoids	Within 4 Weeks
Systemic chemotherapeutic agents	Within 5 half-lives
Investigational drugs or treatments	Within 5 half-lives
Biologics (such as monoclonal antibodies) and biological immunoresponse modifiers (such as, but not limited to interferons) with immunosuppressive/immunomodulatory mechanism of action	Within 5 half-lives
Medications that are potent inh bitor and/or inducer of cytochrome P450 1A2 and 3A4 (see Appendix 6 for examples of such medications)	Within 2 Weeks
Grapefruit juice: more than 1 glass (i.e. 240 mL) per day	Within 2 Weeks
At or adjacent to the target treatment lesions or on the distant untreated lesion: Any surgical procedures other than biopsies related to CTCL diagnosis or follow-up Any topical treatment other than bland moisturizers (creams, lotions, emollients, etc.).	Within 2 Weeks

23. For subjects accepting full PK assessments and/or biopsies: past history of coagulation disorder with abnormal International Normalized Ratio (INR).
24. The subject is vulnerable (such as deprived from freedom) as defined in Section 1.61 of International Conference on Harmonisation. (ICH) Guideline for Good Clinical Practice (GCP).
25. Adults protected by the law (adults under guardianship, or hospitalized in a public or private institution for a reason other than the clinical trial).

5.3.3 Withdrawal criteria in case of disease progression

In case of progressive disease, confirm after 4 Weeks before discontinuing the subject from the trial. Only unequivocal progressive disease confirmed by the investigator does not need confirmation. Progressive disease is defined as:

1. a ≥25% increase in skin disease from baseline based on mSWAT; There will be an exception to subjects with stage IA where ≥25% on mSWAT from baseline may not be clinically meaningful as long as the BSA affected with the disease is <10%.
2. OR occurrence of new tumors (T3) in subjects with T1, T2 or T4 only skin disease;
3. OR loss of response: in those with complete or partial response, increase of mSWAT score of greater than the sum of nadir plus 50% baseline score.
   Nadir is defined as the lowest skin score (best response)

Subjects with relapse between Baseline and Week 36 should remain in the trial, relapse being defined as "any disease recurrence in subjects with complete response based upon baseline mSWAT" (see Appendix 2). Subjects requiring other CTCL therapies will be withdrawn. Should the subject relapse between Week 36 to Week 72, the subject will be early terminated from the study.

5.4 Previous and concomitant therapies

5.4.1 Definition

Previous therapies are defined as therapies that have been stopped before the screening visit. Only relevant therapies will be recorded in the eCRF:

all therapies for CTCL

all therapies used within the last 6 months

all other treatments that may interfere with the trial results in the investigator's opinion

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical trial, or
- any new therapies received by the subject since the screening visit

5.4.2 Categories

The following two categories are to be considered for previous and concomitant therapies:

- Drugs/therapies including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers, X-rays, etc.

5.4.3 Recording

Previous and concomitant therapies are to be recorded on the Drugs/Therapies form (for drugs/therapies) and/or on the Medical and Surgical Procedures form (for medical/surgical procedures) in the eCRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an adverse event (AE). A corresponding Adverse Event Form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

5.4.4 Authorized concomitant therapies

Unless listed under the exclusion criteria (Section 5.3.2) or in prohibited concomitant therapies (see Section 5.4.5), all therapies are authorized.

To manage predicted adverse events such as fever, subjects may take acetaminophen as required for symptomatic relief, at a dose of no more than 3 g/day (refer to local prescribing information of acetaminophen).

Subjects may apply a moisturizer at the discretion of the investigator. However during active treatment periods, moisturizer should not be applied on the target lesions within one hour before or after application of the trial drug and must not be used on the target lesions within 48 hours of trial visits at Week 12, 24, 28, 32, 36, 48, 60 and 72.

5.4.5 Prohibited concomitant therapies

The following therapies are prohibited because they may interfere with the efficacy and/or safety (for example interaction with the trial drug(s) metabolism) assessment of the trial drug(s):

- Imiquimod
- Immune response modifiers (other than imiquimod)

- Interferon inducers
- Chemotherapeutic agents (systemic and topical)
- Biologic agents including interferon
- Systemic retinoids
- Systemic corticosteroids
- Investigational drugs or treatments
- Total body electron beam radiation
- Local radiation therapy
- UVB therapy
- PUVA
- Photopheresis
- Systemic immunosuppresive drugs
- Any topical treatment other than bland moisturizers (creams, lotions, emollients, etc.) at or adjacent to the target treatment lesions or on the distant untreated lesion.
- Any surgical procedures other than biopsies related to CTCL diagnosis or follow-up, at or adjacent to the target treatment lesions or on the distant untreated lesion
- Medications that are potent inhibitor and/or inducer of cytochrome P450 1A2 and 3A4 (see Appendix 6 for examples of such medications)
- Grapefruit juice

Subjects should not shower sooner than 8 hours after application of the gel.

Subjects must take adequate sun avoidance measures, i.e. avoiding direct sunlight where possible and covering treated lesions with clothing if going outside. Use of sunscreen on the target lesions (treated lesions and the distant untreated lesion) is forbidden.

If a prohibited therapy becomes a necessary treatment for the safety or best interest of the subject, The Sponsor should be notified to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives a prohibited therapy during the clinical trial, The Sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical trial.

5.5 Procedures/Reasons for subject discontinuation

An Investigator may decide to discontinue a subject from the clinical trial for safety reasons.

Although the importance of completing the entire clinical trial should be explained to the subject by the clinical trial personnel, any subject is free to discontinue participation in this clinical trial at any time and for whatever reason, specified or unspecified, and without any prejudice. No

constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated.

When a subject does not complete the clinical trial, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Early Termination visit (see Table 2) should be completed for all subjects discontinuing the clinical trial and the appropriate Case Report Form of the eCRF should be completed.

All discontinuations and the reason for discontinuation are to be documented by the Investigator on the Exit Form.

For discontinuation due to an AE, the Adverse Event Form is to be completed. The Investigator should also ensure that the subject receives suitable therapy for the AE.

A subject who has been randomized and assigned a randomization number cannot be replaced by another subject if he/she discontinues the clinical trial for any reason.

The Sponsor may also decide to prematurely terminate or suspend a subject's participation in the clinical trial.

Potential reasons for discontinuation, as listed on the Exit Form, are defined below:

Pregnancy:	**Withdraw the Subject from the trial and follow the procedure described in Section 7.2.4.2.4**
Progressive disease:	Disease progression is defined in section 5.3.3. The Investigator must assess disease progression. If subject believes the disease has progressed but not the opinion of the Investigator, mark "withdrawal by subject" and document this reason in the comment section of the eCRF Exit Form.
Adverse Event:	Complete an Adverse Event Form.
Withdrawal by Subject:	Includes consent withdrawal, subject relocation, schedule conflicts, etc. Does not include AE. Explain the reason for withdrawal in the comment section of the eCRF Exit Form.
Protocol Deviation:	Explain the deviation in the comment section of the eCRF Exit Form.
Lost to Follow-up:	Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the eCRF Exit Form.
Other:	This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the eCRF Exit Form.

If reason for discontinuation is “withdrawal by subject” or “other”, the subject will be questioned to rule out the possibility of an AE (this should be documented). If the AE led to discontinuation, then “adverse event” should be chosen as the reason for discontinuation, rather than “withdrawal by subject” or “other”.

6 CLINICAL SUPPLIES

6.1 Clinical supply identification and use

6.1.1 Trial drug(s) description

Table 6 Description and usage of the trial drug(s)

	Investigational product	Comparator Product
Trade Name or Equivalent	Not applicable	Not applicable
Name of Drug Substance	Resiquimod (4-amino-α,α-dimethyl-2-ethoxymethyl-1*H*-imidazo [4,5-*c*] uinolone-1-ethanol)	Not applicable
Name of Drug Product	CD11301 0.03% gel or CD11301 0.06% gel	CD11301 gel placebo
Internal Code	CD11301	CD11301
Pharmaceutical Form	gel	gel
Strength /Concentration*	0.03% and 0.06%	0% (placebo)
Formula number	0.03% : 0392.0002 0.06%: 0392.0003	0392.0001P
Packaging (type and size)	30 g tubes	30 g tubes
Storage Conditions	Store below 25°C (77°F); do not freeze or refrigerate	Store below 25°C (77°F); do not freeze or refrigerate
Dosage (total daily dose)	A thin layer (approximately 5 mg/cm^2) of resiquimod gel will be applied on 5% BSA up to a maximum of 4.25g in Cycle 1 and in Cycle 2, 5% BSA with a gradual increase to 10% BSA with a maximum dose of 8.5g.	A thin layer (approximately 5 mg/cm^2) of placebo gel will be applied on 5% BSA up to a maximum of 4.25g only in Cycle 1.
Route	topical	

Dose Regimen	▪ Cycle 1: Each active treatment arm will receive resiquimod gel at concentrations of 0.03% or 0.06% or placebo gel. Treatment will be applied on the up to 5 treated target lesions covering up to 5% of BSA, in the morning, 3 times per Week (non-consecutive days) for the first 2 Weeks, then 5 times per Week for additional six Weeks if tolerability permits. Rules for treatment adjustment are in Section 6.4. After 8 Weeks Cycle 1 treatment period, subjects will have a four-Week treatment free period. ▪ Cycle 2: Each active treatment arm will continue to receive resiquimod gel at the same concentrations of 0.03% or 0.06% they were randomized to in Cycle 1. In Cycle 2, subjects receiving placebo in Cycle 1 will be switched to resiquimod gel 0.03%. Treatment will be applied on the same treated target lesions as in Cycle 1. In addition it may be applied on other lesions covering up to 5% of BSA (inclusive of all treated target lesions) in the morning, three times per Week (non-consecutive days) for two Weeks, then on up to 10% of BSA (inclusive of all treated target lesions) in the morning, five times per Week (consecutive or non-consecutive days) for six Weeks, if tolerability permits. Rules for treatment adjustment are in Section 6.4. Subjects will then have a four-Week treatment free washout period. ▪ Follow-up period: Further to the Cycle 2 of treatment, subjects will enter an additional 12-Week follow-up period free of treatment with monthly visits (Week 28, Week 32 and Week 36). At Week 36, complete responders, as determined by Investigator from the mSWAT Skin Involvement assessment, will continue with a 36-Week follow up period free of treatment with visits every 3 months and phone calls in between. Subjects will be followed until Week 72 or relapse, whichever comes first.
Duration of administration	Two cycles consisting of eight Weeks active trial treatment in each cycle.
Location of Treated Area	The target untreated lesion, assessed to investigate a potential remote (systemic) effect, as well as the treated lesions must be below the neck and must not involve the genitalia, intertriginous areas, antecubital areas, or palms and soles. Treatment must not be applied to mucous membranes or to skin areas infected and/or ulcerated. Treated lesions should preferably be separate and distinct from others.

*Note: 0.03 % (w/w) corresponds to concentration of 0.3 mg/g
0.06 % (w/w) corresponds to concentration of 0.6 mg/g

CCI

CCI

[redacted]

6.1.4 Randomization number

A randomization number will be allocated to each eligible subject at baseline by the IRT system.

6.1.5 Instructions for use and administration

Detailed instructions for use will be provided to the subjects and sites in a specific document. Gloves should be used by the subject or designee when applying the IP.

Briefly, the Investigator or designee will clearly identify the target lesions to be treated. The investigator will determine the dose to be applied on each treated target lesion based on its surface area. In Cycle 1, treatment will be applied up to 5% BSA and the maximal daily dose should not exceed 4.25 g. In Cycle 2, treatment will initially be 5% for 2 Weeks, increasing to 10 % BSA with the maximal daily dose not to exceed 8.5g. The Investigator or designee will also clearly identify the lesion to be left untreated (target untreated lesion).

To determine the area of the lesions, the longest diameter and the longest diameter perpendicular to this diameter of each lesion will be measured to the nearest millimeter. The lesion area will be the product of these two diameters.

Using gloves, a thin layer of gel will be applied on defined lesions. The total dose to be applied will be defined for each subject one site the first application day. The dose should not exceed the one defined at site.

For the Subject who agree to do the full PK profile, application of trial product will be done on site for the three PK days (Weeks 12, 14 and 20). The applied dose and BSA treated should be recorded for each PK subjects at these three PK days.

The trial drug will be applied in the morning. Subjects should not shower sooner than 8 hours after application of the gel.

Subjects must take adequate sun avoidance measures, i.e. avoiding direct sunlight where possible and covering treated lesions with clothing if going outside. Use of sunscreen on the target lesions (treated lesions and the distant untreated lesion) is forbidden.

CCI

[redacted]

6.3.1 Accountability

Upon receipt of the trial drug(s), the product dispenser(s) will maintain accurate records of the trial drug(s) delivery to the clinical trial center, the inventory at the clinical trial center, the dispensed and returned trial drugs for each subject, the reconciliation of all trial drug(s) received from the Sponsor/CRO, and the return to the Sponsor/CRO of used and unused trial drug(s).

The product dispenser is required to sign the appropriate form upon receipt and inspection of the supplies, fax the signed copy to the Sponsor/CRO and retain the receipt within the clinical trial file.

All used and unused trial drug(s) will be appropriately inventoried by the monitor. Depending on each site's trial drug handling regulations the drug should be returned to the Sponsor/CRO for further reconciliation, weighting/counting if appropriate, and destruction as instructed by the Sponsor/CRO. If not possible, then the trial drug will be destroyed at the site and documented appropriately.

All trial drug(s) sent to the Investigator/Institution will be accounted for. No unauthorized use is permitted.

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[redacted]

6.3.4 Treatment compliance management and record

Subject will maintain records of their application compliance per target treated lesion throughout the course of the trial by using a dosing diary. Subjects will be instructed on how to complete the dosing diary, recording the days which drug was applied, and the amount prescribed for each target treated lesion. Dosing diaries should be reviewed by the study personnel for missed applications between dispensing visits. This information will be documented in the eCRF by recording the number of missed application compared to what has been prescribed.

Subjects will be questioned regarding the study drug application technique and use of any additional topical or systemic medications (including OTC products) indicated for the relief of local signs and/or symptoms related to local tolerability and these will be documented in the eCRFs.

6.4 Dose modification

The following rules for dose adjustment/discontinuation are defined in case of local or systemic adverse event:

In case of a Grade 2 related adverse events from the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 which cannot be controlled by symptomatic treatment: stop treatment until the AE severity is back to CTCAE Grade ≤1.

Treatment should be restarted with applications 3 times per Week for 2 Weeks, then increased to 5 times a Week for the remaining time in the active treatment period.

If CTCAE Grade 3 related adverse events, stop the treatment until the AE severity is back to CTCAE Grade ≤1. The decision to re-challenge is left to the medical judgment of the Investigator (e.g. depending on the type of adverse event).

Photographs of cutaneous AEs will be taken. **For cutaneous AEs, dose modification should be done on the involved lesion only, not on all treated lesions**.

In the event a lesion resolves within the first 8 Weeks of treatment, treatment should continue to until the end of Cycle 1.

In case a lesion is cleared (complete response according to 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 (as defined in Appendix 2) will be followed for 12 Weeks to assess duration of response and time to disease progression.

6.5 Blinding

6.5.1 Verification of blinding

Although minimal differences in trial products viscosity may be observed, depending on the active ingredient concentrations, the trial design is considered double-blind based on the following rationale:

1. The trial products (placebo, 0.03% and 0.06% gel) will be filled in the same packaging material.
2. The subjects will not have in hands 2 different products at a time.
3. The trial products should be dispensed by and returned to the product dispenser, but in no case to the Investigator and/or other evaluator(s). The trial personnel dispensing the trial products will instruct the subject to not discuss the appearance of the trial product with the Investigator and/or other evaluator(s).
4. The randomization list will be managed by the IRT system with restricted access to authorized personnel only.

6.5.2 Unblinding during the clinical trial

Emergency un-blinding during the clinical trial may be required during the course of the trial to assist in the proper treatment of an AE or for regulatory reasons (e.g. for expedited safety reporting).

A system to allow to break the blind will be available for Investigators through the IRT. In such an emergency, the Investigator will only break the blind for the subject involved.

The Investigator must notify the CSO immediately in the event of such an emergency (see contact details in Section 7.2.4.2.2). If possible, the Investigator should notify the CSO before breaking the blind in order to discuss this decision. The Investigator is required to document each case of emergency unblinding on the appropriate form (provided by the Sponsor).

The data initially reviewed by the IDMC will be partially blinded using letter codes (A, B, C) for treatment groups; however the IDMC may request unblinding to the independent data analyst if necessary, on a case by case basis (specific subjects only) or at the group level.

Bioanalytical local un-blinding:

Sample assay will only be performed on samples from subjects treated with resiquimod gel. Prior to sample assay, local unblinding at Sponsor Bioanalytical Department will be restricted to the Bioanalytical Study Director and his/her direct collaborators, in order to select the appropriate samples for the assay. Bioanalytical results will only be disclosed, after database lock, following a formal authorization provided by the Clinical Project Manager.

7 CLINICAL TRIAL ASSESSMENT

7.1 Efficacy assessments

7.1.1 Efficacy measurements

The same clinician/evaluator is to perform the assessment at Screening, Baseline and Week 12. With all other visits, if not possible, the Sponsor recommends that evaluations between the primary and subsequent evaluator overlap for at least one visit (i.e., both evaluators should examine the subject together and harmonize their assessment). This must be documented in the source and in the appropriate comments section of the eCRF.

Evaluators must be trained by a Sponsor's representative prior to performing an efficacy assessment.

Untrained evaluators are not allowed to perform these assessments.

7.1.1.1 Modified Composite Assessment of Index Lesion Severity (mCAILS)

mCAILS instrument will be used to make two different assessments: one on the target treated lesions and one on the untreated distant target lesion (Heald et al, 2003) (Olsen et al, 2011) (Duvic et al, 2001 (b)). mCAILS will be assessed according to the schedule of assessments (see Table 2).

The target lesions (treated and untreated) should be clearly identified using photography by the Investigator beginning with the screening.

See Appendix 1.

7.1.1.2 Modified Severity-Weighted Assessment Tool (mSWAT)

The mSWAT composite score will be used to assess the whole body involvement (Olsen et al, 2011) according to the schedule of assessments (see Table 2).

See Appendix 2.

7.1.2 Efficacy endpoints

Primary

- Overall response rate (complete and partial response) of target lesions at Week 12: based upon Modified Composite Assessment of Index Lesion Severity (mCAILS) score at Week 12. Complete Response (CR) is defined as a score of '0' on the mCAILS scale. Partial response (PR) is defined as a reduction of at least 50% from Baseline, but less than 100% in the mCAILS scale.

Secondary

- Overall response rate (CR and PR) based upon mSWAT composite score at Week 12. CR is defined as 100% clearance of skin lesions and PR as 50 to <100% clearance from baseline without new tumors (T3) in subjects with T1, T2 or T4 only skin disease.
- Time to overall response (CR or PR) response based on mCAILS score.
- Duration of overall response (CR or PR) based on mCAILS score.
- Time to progressive disease using mSWAT
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7.2 Safety assessment

A safety assessment will be conducted for all subjects at the screening visit (from the Informed consent signature) and every subsequent visit/phone calls. The safety parameters are AEs, physical examination and body weight, vital signs assessments, electrocardiograms, and laboratory safety tests.

7.2.1 Physical examination and vital signs

7.2.1.1 Physical examination

Physical examination will be performed at all trial visits except phone calls.

The following body systems should be evaluated as "normal" or "abnormal" by the Investigator or designee, at the screening visit and at all trial visits. Abnormalities will be recorded on the eCRF.

- Skin
- Lungs
- Abdomen
- Eyes/ears/nose/throat
- Neurological function
- Musculoskeletal system
- Lymph nodes
- Cardiovascular system

The Investigator or designee may choose to investigate any other sign that he/she observes during the physical examination and should assess all abnormal findings for clinical significance. All clinically significant abnormal findings at the screening visit will be recorded in the Medical History.

For any clinically significant changes from the screening visit, an AE is to be recorded.

7.2.1.2 Vital signs

Vital signs (pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP), temperature, and respiratory rate) will be collected at all trial visits, except phone calls. Evaluation of vital signs will be performed after 5 minutes rest in the sitting position.

All abnormal values at the screening visit identified as clinically significant by the Investigator or designee, will be recorded in the Medical History form.

For any clinically significant changes from the screening visit, an AE is to be recorded.

7.2.1.3 Height, Weight, and Body Mass Index (BMI)

Height will be measured at the screening visit. Body weight (BW) will be measured at all trial visits except phone calls in order to calculate the BMI.

7.2.2 Electrocardiograms

Electrocardiograms (ECG) will be performed according to the schedule of assessments (see Table 2) and reviewed by the Investigator or deputy.

In addition, for subjects selected for full PK assessment, at Week 20, serial ECGs will be performed at the time of the trial drug application (pre-dose) and 2, 4, 6, 8, 12 and 24 hours after the trial drug application.

The subjects should be kept in the supine and resting position for at least 10 minutes prior to obtaining the ECG in order to achieve the steady heart rate. The ECG will precede the PK blood draw.

All ECG will be sent for review to a Central Independent Reviewer.

7.2.3 Laboratory safety tests

The following safety lab tests will be performed according to the schedule of assessments (see Table 2):

Hematology:

Hematology: White Blood Cell (WBC) count with differential, red blood cell count, hemoglobin, hematocrit, reticulocyte count, mean cell volume, INR and platelet count.

Blood chemistry:

Albumin, creatinine, uric acid, urea nitrogen, glucose, sodium, potassium, chloride, GGT, ALP (alkaline phosphatases), AST, ALT and bilirubin (total and conjugated), triglycerides.

Urinalysis:

Glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocytes.

Thyroid function tests:

Thyroid Stimulating Hormone (TSH), T3, T4, and anti-thyroid antibodies (thyroid peroxidase and thyroglobulin antibodies) according to the schedule of assessments (see Table 2).

The screening visit laboratory values must be available prior to the Baseline visit.

The Investigator or a medically qualified Sub-Investigator must review and evaluate laboratory values for each subject in a timely manner. The Investigator or designee will initial and date all laboratory reports and note directly on the report whether or not each out-of-range laboratory value is clinically significant. An out of range laboratory value should be considered as clinically significant if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation

For each out-of-range laboratory result, the Investigator or designee will enter directly in the eCRF the Investigator judgment on the presence or the absence of a clinical significance.

All clinically significant out-of-range laboratory values for blood and/or urine samples collected at screening, will be recorded in the medical history (report a diagnosis rather than an individual laboratory parameter abnormality whenever possible) and the subject will not be eligible for the trial.

All clinically significant out-of-range laboratory values for blood and/or urine/serum samples collected after screening, are to be reported as an AE if this abnormality was not present at the screening visit or is assessed as having worsened since the screening visit (i.e., there is a significant change from screening).

If the Investigator observes a clinically relevant laboratory test value, the laboratory tests will be repeated as soon as possible and monitored until the values have returned to normal and/or an adequate explanation for the abnormality is found. This does not apply to screening laboratory test values. No retest at screening is allowed (unless in case of damaged samples for instance). *Note that both repeat lab tests and unscheduled visit labs will be placed under the category of "unscheduled visit" as there is no value in differentiating them within EDC.*

In instances when a laboratory abnormality is reported as an AE, whenever possible, the Investigator is to provide a diagnosis rather than reporting individual laboratory abnormalities.

A summary of sample volumes and the number of blood samples is detailed in Appendix 5.

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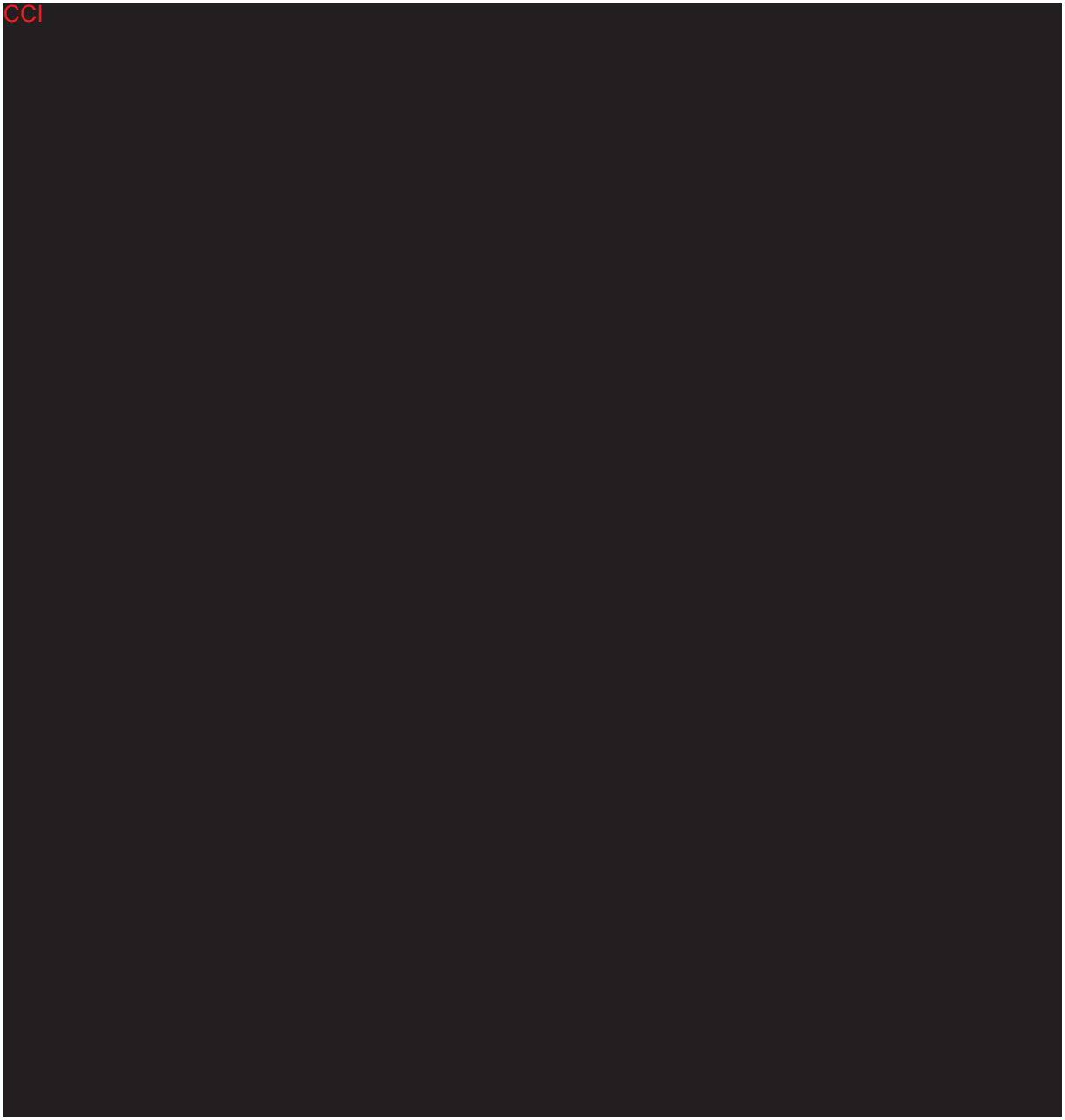

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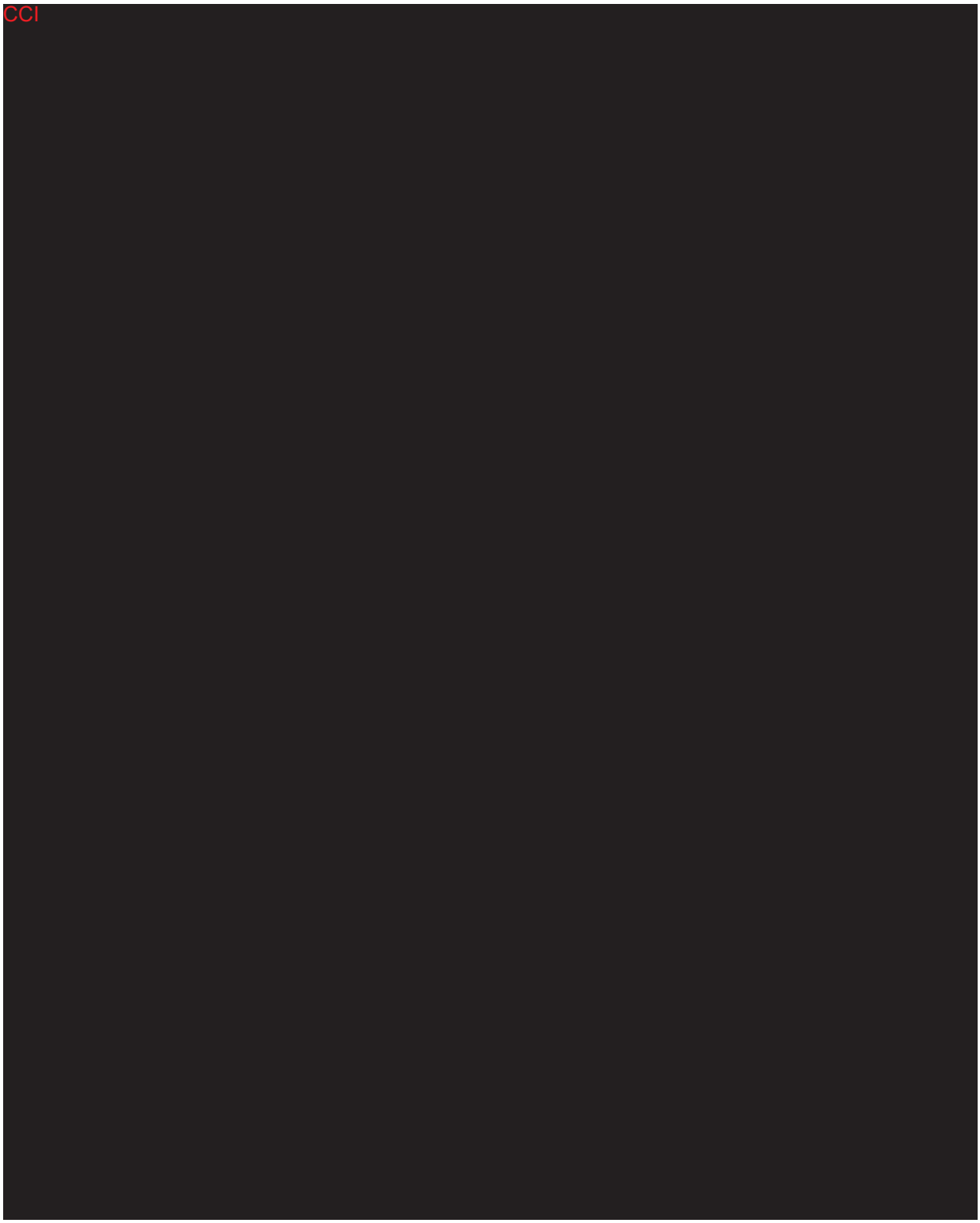

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7.3 Pharmacokinetic assessments

Blood samples for complete pharmacokinetic (PK) assessments of resiquimod and five (5) metabolites (S-28371, S-31451, S-32483, S-32899, and S-32544) will be collected from up to 36 subjects (PK subjects) according to the schedule of assessments and PK timepoints (see Table 2 and Table 3).

Blood samples for proof of exposure assessments of resiquimod and five (5) metabolites will be collected from all subjects according to the schedule of assessments (see Table 2).

7.3.1 Plasma concentration

Resiquimod and the five (5) metabolites plasma concentrations will be determined by a CRO using validated LC/MS-MS methods. A bioanalytical plan describing the detail of the bioanalytical work related to plasma samples and acceptance criteria will be written before the beginning of the sample analysis.

7.3.2 Technical procedures for pharmacokinetic biological blood sampling

Blood samples (10 mL) will be collected at each time point. Refer to Appendix 5 for total blood volumes.

Blood samples will be collected into vacutainer tubes containing a lithium heparin additive as an anticoagulant according to the flow chart for pharmacokinetic sampling time presented in Table 3.

The different steps of the blood sample processing will be described in a specific laboratory manual. The plasma samples will be stored at approximately -80C.

The time and date of collection for each sample will be recorded on the eCRF. An attempt will be done to collect the PK samples at the target time points; however, allowed time windows for PK blood sample collection times will be defined in the laboratory manual.

The time of last trial drug application will be recorded in the eCRF.

In order to avoid potential contamination of the blood samples, trial drug applications and blood draws must NOT occur in the same room. Additionally, the blood draw area should be clean and kept away from contact with the trial drugs. The trial personnel must change gloves before performing blood sampling.

7.3.3 Pharmacokinetic analysis

The pharmacokinetic analyses will be carried out under the supervision of the clinical PK group of Galderma S.A.

From the individual plasma concentrations, the pharmacokinetic parameters will be determined by a model independent approach (non-compartmental method). Data from subjects with missing concentration values (missing samples) may be used if pharmacokinetic parameters can be estimated using the remaining data points. In estimating the pharmacokinetic parameters, the Below the Limit of Quantitation (BLQ) plasma concentration will be replaced by the Limit of Quantitation (LOQ).

The following non-compartmental pharmacokinetic parameters for resiquimod and its related metabolites will be determined for each subject, when appropriate, if sufficient plasma concentrations are above the limit of quantification:

Table 7 Pharmacokinetic parameters

C_{max}	The observed peak drug concentration
T_{max}	The time at which C_{max} occurs.
C_{trough}	The residual concentration of the drug (pre-dose level)
C_t	The plasma concentration the drug at the time of blood sampling
AUC_{0-24h}	Area under the concentration-time curve calculated by the mixed linear-logarithmic trapezoidal method from T0 up to 24 hours. When appropriate, corrected baseline value will also be reported for AUC_{0-24h}
AUC_{0-t}	Area under the concentration-time curve calculated by the mixed linear-logarithmic trapezoidal method from T0 up to the last quantifiable point. When appropriate, corrected baseline value will also be reported for AUC_{0-t}
AUC_{0-inf}	Area under the plasma concentration-time curve calculated by the mixed linear-logarithmic trapezoidal method from T0 and extrapolated to time infinity as: $AUC_{0-inf}=AUC_{0-t}+ C_{last} / k_{el}$. When the extrapolation represents more than 20%, AUC_{0-inf} and $t_{1/2}$ will not be reported.
$t_{1/2}$	The terminal half-life value ($t_{1/2}$) will be calculated using the equation $ln2/k_{el}$ after the last application

% AUC	Relative AUC_{0-t} OR $AUC_{0-24\ h}$ ratio between resiquimod and its metabolites

Accumulation ratios will be calculated for resiquimod based on the AUC_{0-24h} measured on Weeks 12, 14 and 20.

Table 8 PK parameters to be calculated at each timepoint

Cycle 1 (% 5 BSA)				
Visit	**Week 4 (V4)**		**Week 8 (V5)**	
Proof of exposure in ALL subjects	C_t		C_t	
Cycle 2 – (up to 10% BSA)				
Visit	**Week 12 (V6)[a]**	**Week 14 (V7)[a]**	**Week 16 (V8)**	**Week 20 (V9)[a]**
Complete PK profile (PK subjects)[b]	C_{trough}, C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24h} AUC_{0-inf} , %AUC, $t_{½}$	C_{trough}, C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24h} AUC_{0-inf} , %AUC	C_t	C_{trough}, C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24h} AUC_{0-inf} , %AUC, $t_{½}$,
Proof of exposure in ALL non PK subjects	C_t	C_t	C_t	C_t

a) Application of trial drug done by a trained personal for PK subjects at Week 12, 14 and 20.
b) For subject with specific consent

Descriptive statistics (Mean, Min, Max, standard deviations) will be calculated and reported on each variable.

Additional PK analysis using compartmental methods (i.e. population PK analysis) may also be conducted (if data permits) to assess effect of covariates such as age, weight, gender, ethnicity, and renal clearance.

If possible, the exposure – response relationship, i.e. potential relationship between plasma concentrations of resiquimod or other indicators of disease activity will be explored using PK/PD modeling, as appropriate.

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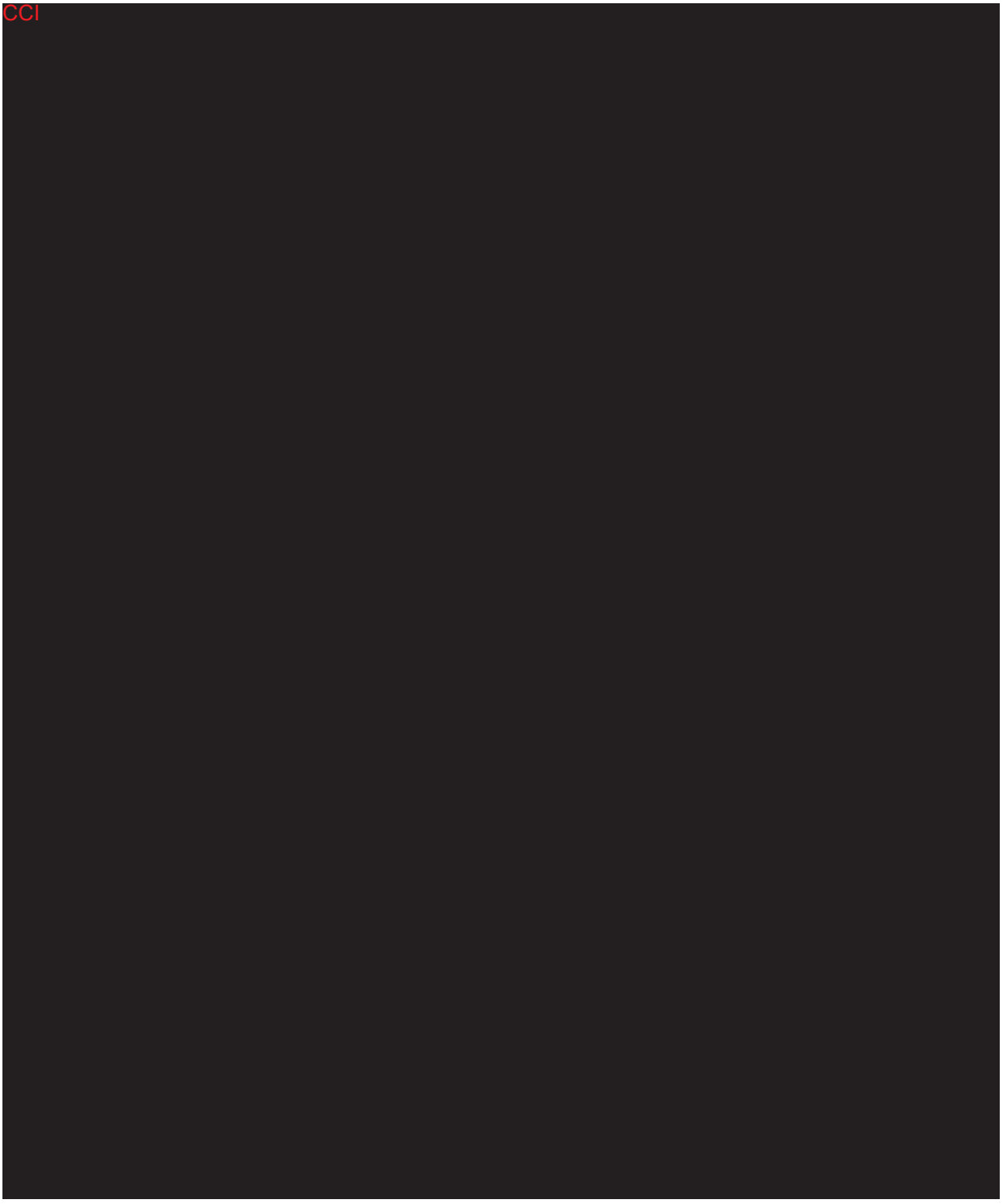

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7.5 Other assessments

7.5.1 Photographs

Photographs will be taken at all sites. Photographs will be taken in order to document the observed effect, according to the schedule of assessments (see Table 2):

Photographs of the lesions chosen for mCAILS assessment (treated lesions and distant lesion)

Photographs of subject BSA involvement: anterior and posterior torso and limb, i.e. from the neck down

7.5.2 Quality of Life Assessment

The Skindex 29 Dermatology Survey of Quality of Life will be filled out by the subjects according to the schedule of assessments (see Table 2) (Chren et al, 1996).

See Appendix 3.

7.5.3 Subject assessments

7.5.3.1 Patient global assessment of improvement

Subjects will assess the global improvement of their whole body according to the schedule of assessments (see Table 2), compared to their condition at baseline, before starting treatment, using a scale from 1 (excellent) to 5 (worse) (see Appendix 4).

7.5.3.2 Pruritus assessment

Pruritus NRS (Numeric Rating Scale) is a scale to be used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours.

Subjects will be asked the following questions in their local language:

- For average itch intensity: "on a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst imaginable itch', how would you rate your itch overall during the previous 24 hours?"
- For maximum itch intensity: "on a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst imaginable itch', how would you rate your itch at the worst moment during the previous 24 hours?"

See Appendix 4.

8 DESCRIPTION OF CLINICAL TRIAL VISITS

Please refer to the schedule of assessments table in the synopsis (Table 2).

A written, signed Informed Consent Form (ICF), HIPAA if applicable, must be obtained prior to performing any clinical trial-related evaluations and/or procedures. In addition, for optional assessments (eg. biopsies, full PK assessments, cellular immunology), a specific consent must be obtained. The subject must be provided with a fully completed, dated and signed copy of the consent form(s).

8.1.1 Screening visit [Day -28 to Day -15]

A maximum of 28 days is allowed between Screening and the first trial drug administration at Baseline. The minimum time period between Screening and Baseline is the amount of time necessary for the Investigator to receive laboratory test results from the Screening visit. For women of childbearing potential, there must be at least 15 days between Screening and Baseline Visit (for UPT reason).

At the Screening visit, the Investigator or designee will:

1. Review and explain the nature of the trial to the subject, particularly the prohibited activities and constraints (e.g., restrictions in the use of topical and systemic medications).
2. Obtain the signed and dated ICF (including optional sections for PK or PD assessments if applicable) and HIPAA if applicable; provide a fully completed dated and signed copy to the subject.
3. Assign the subject a Subject Identification Number (SIN).
4. Collect information regarding demographics and medical history.
5. Record previous therapies/procedures, including an exhaustive list of all previous CTCL therapies/procedures.
6. Record all concomitant therapies and procedures.
7. Confirm clinical diagnosis of CTCL stage IA, IB, or IIA, including documentation of a skin biopsy within the last twelve (12) months with histological findings consistent with CTCL.

If one is not available, a (non-target lesion) skin biopsy may be performed at the Screening visit for confirmation.

8. Perform a physical examination including height and weight, and calculate the body mass index (BMI) and Body surface area (BSA). Perform vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
9. Perform an ECG.
10. Confirm that the subject meets inclusion/exclusion criteria (all criteria except those depending on laboratory analyses).
11. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
12. Take photographs.
13. Complete serum pregnancy test if the subject is a female of childbearing potential.
14. Collect urine for urinalysis and a blood sample for hematology and blood chemistry (see laboratory manual).
15. Collect a blood sample for thyroid function tests (see laboratory manual).
16. Complete the Subject Screening Log.
17. Record any AEs on the eCRF. AEs will be collected starting from the time of Informed Consent signature.
18. Schedule the Baseline visit within maximum 28 days. For women of childbearing potential, there must be at least 15 days between Screening and Baseline Visit (for UPT reason).

8.1.2 Baseline visit [Week 0]

At the Baseline visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Check laboratory results (hematology, blood chemistry, urinalysis and thyroid function tests) from the Screening visit against the exclusion criteria.
3. Complete urine pregnancy test if the subject is a female of childbearing potential (this includes females who were pre-menstrual at Screening but have since begun menses).
4. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
5. Confirm subject meets inclusion/exclusion criteria. Enroll the subject in the clinical trial using the IRT system.

6. Confirm the CTCL stage IA, IB, or IIA, if skin biopsy was performed at the screening visit.
7. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
8. Ask subject to complete the Skindex 29 questionnaire and pruritus assessment.
9. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
10. Take photographs.
11. Collect urine for urinalysis and a blood sample for hematology and blood chemistry (see laboratory manual).
12. Collect blood sample for immune cell dynamic analysis (see laboratory manual).
13. Collect blood sample for cellular immunology, if applicable (see laboratory manual).
14. Collect skin biopsies (see laboratory manual), if applicable.
15. Dispense trial drug, ruler and diary to the subject and provide written/oral instructions for trial drug application. The first application will be done on site under the supervision of the product dispenser.
16. Complete the Subject Enrollment Log.
17. Schedule the next visit in 2 Weeks.

8.1.3 Week 2 visit

At the Week 2 visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
3. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
4. Perform an ECG.
5. Ask subject to complete a pruritus assessment.
6. Collect urine for urinalysis and a blood sample for hematology and blood chemistry (see laboratory manual).
7. Collect returned trial drug. Review the subject’s compliance with the trial drug.

8. Dispense trial drug and ruler to the subject and provide written/oral instructions for trial drug application.
9. Schedule the next visit in 2 Weeks.

8.1.4 Week 4 and Week 16 visits

At the Week 4 and Week 16 visits, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
3. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
4. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
5. Ask subject to complete a pruritus assessment.
6. At Week 4 only: perform an ECG.
7. Collect a blood sample for PK assessment (proof of exposure) and record the date and time of last trial product application and the time of blood collection.
8. Collect blood samples for cellular immunology, if applicable (see laboratory manual).
9. Collect returned trial drug. Review the subject’s compliance with the trial drug.
10. Dispense trial drug and ruler to the subject and provide written/oral instructions for trial drug application.
11. Schedule the next phone call in 2 Weeks.

8.1.5 Week 6, Week 10, Week 18 and Week 22 phone calls

Subjects will be called by phone and asked about potential adverse events and potential changes in concomitant therapies/procedures. On a case by case basis, depending on the Adverse Event, an unscheduled visit may be organized.

Pruritus assessment will also be performed during phone calls.

Schedule the next visit in 2 Weeks.

8.1.6 Week 8 visit

At the Week 8 visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
3. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
4. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
5. Perform an ECG.
6. Ask subject to complete a pruritus assessment.
7. Collect urine for urinalysis and a blood sample for hematology and blood chemistry (see laboratory manual).
8. Collect a blood sample for thyroid function tests (see laboratory manual).
9. Collect a blood sample for PK assessment (proof of exposure) and record the date and time of last trial product application and the time of blood collection.
10. Collect blood sample for immune cell dynamic analysis (see laboratory manual).
11. Collect blood sample for cellular immunology, if applicable (see laboratory manual).
12. Collect skin biopsy (see laboratory manual), if applicable.
13. Collect returned trial drug and diary. Review the subject’s compliance with the trial drug.
14. Schedule the next visit (phone call) in 2 Weeks.

8.1.7 Week 12 visit

At the Week 12 visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate, on the corresponding eCRF form(s).
2. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
3. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
4. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
5. Perform an ECG.
6. Evaluate the CTCL stage IA, IB, or IIA.
7. Ask subject to complete the Skindex 29 questionnaire and pruritus assessment.
8. Ask the subject to perform a Global Assessment of Improvement.
9. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
10. Take photographs.
11. Collect urine for urinalysis and a blood sample for hematology and blood chemistry (see laboratory manual).
12. For non-PK subjects: collect a blood sample for PK assessment (proof of exposure) and record the date and time of last trial product application and the time of blood collection.
13. Collect blood samples for immune cell dynamic analysis (see laboratory manual).
14. Collect blood samples for cellular immunology, if applicable (see laboratory manual).
15. Dispense trial drug, ruler and diary to the subject and provide written/oral instructions for trial drug application.
16. For PK subjects:
    - collect a blood sample just before product application (pre-dose sample),
    - apply the trial drug, record the applied dose and the BSA treated and the time of application,
    - collect a blood sample 2, 4, 6, 8, 12, 24 and 48 hours after product application.
17. Schedule the next visit in 2 Weeks.

8.1.8 Week 14 visit

At the Week 14 visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
3. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
4. Perform an ECG.
5. Ask subject to complete a pruritus assessment.
6. Collect urine for urinalysis and a blood sample for hematology and blood chemistry (see laboratory manual).
7. For non-PK subjects: collect a blood sample for PK assessment (proof of exposure) and record the date and time of last trial product application and the time of blood collection.
8. Collect returned trial drug. Review the subject’s compliance with the trial drug.
9. Dispense trial drug and ruler to the subject and provide written/oral instructions for trial drug application.
10. For PK subjects:
    - collect a blood sample just before product application (pre-dose sample),
    - apply the trial drug and record the applied dose and the BSA treated and the time of application,
    - collect a blood sample 2, 4, 6, 8, 12, and 24 hours after product application.
11. Schedule the next visit (phone call) in 2 Weeks.

8.1.9 Week 20 visit

At the Week 20 visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate, on the corresponding eCRF form(s).
2. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
3. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
4. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
5. For non-PK subjects: perform an ECG.
6. Ask subject to complete a pruritus assessment.
7. Collect urine for urinalysis and a blood sample for hematology, blood chemistry (see laboratory manual).
8. Collect a blood sample for thyroid function tests (see laboratory manual).
9. For non-PK subjects: collect a blood sample for PK assessment (proof of exposure) and record the date and time of last trial product application and the time of blood collection.
10. Collect blood sample for immune cell dynamic analysis (see laboratory manual).
11. Collect blood sample for cellular immunology, if applicable (see laboratory manual).
12. Collect returned trial drug and diary. Review the subject's compliance with the trial drug.
13. For PK subjects:
    - collect a blood sample just before product application (pre-dose sample),
    - apply the trial drug and record the applied dose and the BSA treated and the time of application,
    - collect a blood sample 2, 4, 6, 8, 12, 24, 48 and 72 hours after product application,
    - perform ECG **before** the blood sampling at the same timepoint windows (except 48 and 72 hours hours).
14. Schedule the next visit (phone call) in 2 Weeks.

8.1.10 Week 24 visit

At the Week 24 visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate, on the corresponding eCRF form(s).
2. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
3. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
4. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
5. Perform an ECG.
6. Evaluate the CTCL stage IA, IB, or IIA.
7. Ask subject to complete the Skindex 29 questionnaire and pruritus assessment.
8. Ask the subject to perform a Global Assessment of Improvement.
9. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
10. Take photographs.
11. Collect urine for urinalysis and a blood sample for hematology, blood chemistry (see laboratory manual).
12. Collect skin biopsies (see laboratory manual), if applicable.
13. Schedule the next visit in 4 Weeks.

8.1.11 Week 28 and Week 32 visits

At the Week 28 and Week 32 visits, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate, on the corresponding eCRF form(s).
2. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.

3. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
4. Ask subject to complete a pruritus assessment.
5. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
6. Schedule the next visit in 4 Weeks.

8.1.12 Week 36 visit

At the Week 36 visit, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
3. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
4. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
5. Evaluate the CTCL stage IA, IB, or IIA.
6. Perform an ECG only if the Week 24 ECG was abnormal.
7. Ask subject to complete the Skindex 29 questionnaire and pruritus assessment.
8. Ask the subject to perform a Global Assessment of Improvement.
9. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
10. Take photographs.
11. Collect urine for urinalysis and a blood sample for hematology, blood chemistry (see laboratory manual).
12. If the subject is not a complete responder on mSWAT, complete the Exit Form and exit the subject from the study. If the subject is a complete responder, as determined by the Investigator from mSWAT Skin Involvement assessment, continue with the follow up period for an additional 36 Weeks. Should the subject relapse prior to Week 72, the subject will be exited from the study as an Early Termination visit.

8.1.13 Week 40, Week 44, Week 52, Week 56, Week 64, and Week 68 phone calls

Subjects will be called by phone and asked about potential adverse events and potential changes in concomitant therapies/procedures. On a case by case basis, depending on the Adverse Event, an unscheduled visit may be organized.

Pruritus assessment will also be performed during phone calls.

Schedule the next visit in 4 Weeks.

8.1.14 Week 48 and 60 visit

At Week 48 and 60 visits, the Investigator or designee will:

1. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
2. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
3. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
4. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
5. Evaluate the CTCL stage IA, IB, or IIA.
6. Ask subject to complete the Skindex 29 questionnaire and pruritus assessment.
7. Ask the subject to perform a Global Assessment of Improvement.
8. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
9. Take photographs.
10. Collect urine for urinalysis and a blood sample for hematology, blood chemistry (see laboratory manual).
11. If the subject relapses, subject should be discontinued from the study and an early termination visit should be completed.

8.1.15 Final visit (Week 72) / Early Termination (ET) visit

At the Final visit / ET, the Investigator or designee will:

12. Ask the subject about AEs using an open-ended question, such as “Have you noticed any change in your health since the last visit?” Record all events, as appropriate, on the corresponding eCRF form(s).
13. Complete urine pregnancy test (or serum) if the subject is a female of childbearing potential (this includes females who were pre-menstrual at the last visit but have since begun menses).
14. Ask the subject about any changes in his/her concomitant therapies/procedures (added, removed or changed) since the previous visit. Record all changes in the source document and the eCRF.
15. Perform a physical examination (including body weight) and vital signs measurements (pulse rate, SBP, DBP, respiratory rate and temperature).
16. Ask subject to complete the Skindex 29 questionnaire and pruritus assessment.
17. Ask the subject to perform a Global Assessment of Improvement.
18. Complete the mCAILS and mSWAT assessments and record score(s) in the source document and eCRF.
19. Take photographs.
20. Collect urine for urinalysis and a blood sample for hematology, blood chemistry (see laboratory manual).
21. Complete the Exit Form.

8.1.16 Unscheduled visits

Subject should be reminded to adhere to the trial schedule, and visits occurring outside of the visit window are not considered as unscheduled visit. Unscheduled visits may be necessary to repeat testing of abnormal laboratory results, complete a test missed during a scheduled visit or for follow-up of AEs (in particular if AE reported during a phone call). Assessments to be conducted at the unscheduled visit will depend on the reason for the visit. In case of unscheduled visit due to an AE reported during a phone call, at minimum, physical examination and vital signs will be collected. Should the subject relapse between Week 36 to Week 72, the subject should be early terminated from the study.

8.2 Subject instructions (other than trial drug(s) administration)

Subjects should not shower sooner than 8 hours after application of the trial drug.

Subjects must take adequate sun avoidance measures, i.e. avoiding direct sunlight where possible and covering treated lesions with clothing if going outside. Use of sunscreen on the target lesions (treated lesions and the distant untreated lesion) is forbidden. Subjects may apply a moisturizer at the discretion of the investigator. However during active treatment periods, moisturizer should not

be applied on the target lesions within one hour before or after application of the trial drug and must not be used on the target lesions within 48 hours of trial visits at Week 12, 24, 28, 32 and 36.

9 STATISTICAL METHODS PLANNED

9.1 Statistical and analytical plans

A Statistical Analysis Plan (SAP) will be developed as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in the sections of the clinical trial protocol below. The SAP will be finalized before breaking the code at Week 36 and only pre-identified sponsor representatives will be unblinded to data at Week 36. An analysis will be performed for the clinical study report after all subjects have completed their Week 36 visit as intended in the original protocol design.

For the amendment 3 protocol, the study is extended to measure time to relapse on complete responders from Week 36 to Week 72. An addendum to the clinical study report will be written after all subjects in the extension period are complete.

9.1.1 Data transformations

Percent reduction in mCAILS and in mSWAT will be calculated.

$AUC_{0\text{-}24h}$ and C_{max} will be logarithmically transformed before analysis.

9.1.2 Populations analyzed and evaluability

The statistical analyses will be performed based on the following subject populations. The Intention-to-Treat (ITT) population will be used for the analyses of efficacy endpoints; and the safety population will be used for the analyses of safety data. The Per Protocol (PP) population will be used for the sensitivity analyses of primary and secondary efficacy endpoints.

9.1.2.1 Intent-to-treat (ITT) Efficacy Population

The ITT Population is defined as comprising all subjects who are randomized. All primary efficacy variables and secondary efficacy variables will be analyzed based on the ITT Population.

Exploratory parameters will be summarized using ITT population, observed data.

9.1.2.2 Per-protocol (PP) Efficacy Population

The PP Population is defined as comprising the ITT subjects who have no major protocol deviations.

9.1.2.3 Safety Population

The Safety Population is defined as comprising the ITT Population subjects who applied the trial drug(s) at least once. All safety data will be summarized based on the Safety Population.

9.1.2.4 PK Population

Subjects with complete PK profiles included in the safety population with no major protocol deviation which can influence the subject's evaluation of pharmacokinetics will be included in the PK analysis.

9.1.2.5 Imputation of missing data

In general, the primary method to handle missing data will be imputing non-response. In addition, LOCF (Last Observation Carried Forward) will be used to impute missing data as sensitivity analyses (corresponding to assigning non-response for binary endpoints) and to the secondary endpoints that are not binary.

9.1.3 Data presentation and graphics

Subject disposition, demographics, baseline characteristics, previous therapies, concomitant therapies, and treatment duration by treatment will be summarized by descriptive statistics.

For statistical analysis purpose, therapies and procedures ongoing at the baseline visit or starting after the baseline visit will be summarized separately from those ending at baseline or before. All efficacy variables will be summarized by treatment at each visit. The categorical variables "Overall response rate (complete and partial response) of target lesions based on mCAILS" and "mSWAT" will be summarized by frequency and percentage for each response category (N, %). The continuous variables "Percent reduction in mCAILS and in mSWAT" will be summarized using means, medians, minimum, maximum, and standard deviations for the data collected at each visit.

For each PK subject, the quantity of gel applied will be expressed in mg /cm^2 for each PK sampling day (i.e. Weeks 12, 14 and 20). This calculation will be derived from the applied dose (mg) and the treated surface area (cm^2). The treated surface area will be derived from the percentage of BSA treated.

Pharmacokinetics parameters (C_{trough}, AUC_{0-24h}, C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf}) at each evaluation day will be summarized by descriptive statistics on the PK analysis population.

Descriptive PK analysis will be done on the C_t collected:

from all non PK subjects at Week 12, Week 14 and Week 20.

for all subjects at Week 4, Week 8 and Week 16.

Shift tables for stage of disease will be displayed presenting Baseline and Week 12 and Week 24 visit. All safety data will be summarized based on the safety population.

Treatment-emergent Adverse Events (TEAEs) will be tabulated in frequency tables by System Organ Class and Preferred Term based on the Medical Dictionary for Regulatory Activities (MedDRA). Summary tables will be provided by cycle.

Additional summary tables will be provided for AEs that are considered serious (SAEs), related to the trial drug(s), and AEs leading to discontinuation. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

In addition, AEs with an onset prior to first trial drug application will be listed separately.

Laboratory data (absolute values and change from baseline) will be summarized by visit and treatment group. In addition, the number and percent of subjects below, within, and above the laboratory reference ranges will be summarized by treatment group. Shift tables will be generated using the reference ranges.

Incidence of Relapse, Patient Global Assessment of Improvement and Change from Baseline in Skindex29 scores (Overall scores as well as emotional, Symptoms, Functioning scores) will be summarized descriptively.

9.1.4 Inferential statistical analyses

Efficacy analysis:

The primary efficacy endpoint is the Overall Response Rate (Complete or Partial Response) based on Modified Composite Assessment of Index Lesions Disease Severity (mCAILS) score at Week 12 for the target lesions. Complete Response is defined as a score of '0' on the mCAILS scale. Partial response is defined as a reduction of at least 50% from Baseline, but less than 100% in the mCAILS scale.

Overall Response Rate based on mCAILS and Overall Response Rate based on mSWAT scores at Week 12 will be analyzed using the Cochran Mantel Haenszel test with the general association statistics, stratified on region (EU vs. US), if applicable.

All inferential statistical tests will be two-sided and will compare each of the two active treatments to placebo, up to Week 12 (end of Cycle 1). To control the overall type I error at 5%, a Hochberg procedure will be used to compare the two doses (0.03% and 0.06%) with placebo. Treatment effect (resiquimod gel vs placebo), p-values and corresponding confidence intervals of the treatment effect (95% of CI and/or 97.5% CI depending on Hochberg procedure) will be presented for each comparison.

Percent reduction in mCAILS (based on treated and untreated lesions separately) and in mSWAT will be analyzed as continuous data at Week 12 using ANCOVA and baseline corresponding mCAILS or mSWAT as covariate and treatment and region as factors.

The time to overall response, the duration of response and the time to progressive disease will be summarized by treatment group using the Kaplan-Meier method. Kaplan-Meier estimates and graphs will be presented.

Primary efficacy data will be summarized at Week 12 by the following subgroups if appropriate:

- By region (EU vs USA)
- By stage of disease (IA vs IIA+IB)
- By Disease Type (mycosis fungoides, folliculotropic), if applicable
- By most frequently used previous therapies for CTCL (phototherapy, steroids)
- By age (<65 years old, ≥65 years old)
- By gender
- By race

Efficacy data post Week 12 will be only descriptively summarized.

PK analysis (PK subjects):

(1) To evaluate the treatment period effect for resiquimod, the following analysis will be performed separately for each treatment group if appropriate:

$AUC_{0\text{-}24h}$ and C_{max} will be submitted, after logarithmic transformation (Ln), to an analysis of variance. The model will include time and subject as factors. The residual error variance will be used to compute 90% confidence intervals of the pairwise differences between time points (Week 12, Week 14 and Week 20 for $AUC_{0\text{-}24h}$, and C_{max}) on the Ln scale. The limits of the intervals will be back-transformed into exponential to obtain 90% confidence intervals of the ratios of geometric means between time points, on the original scale.

(2) To evaluate the treatment effect, the following analysis will be performed separately between group by trial day if appropriate:

$AUC_{0\text{-}24h}$, and C_{max} will be submitted after logarithmic transformation (Ln), to an analysis of variance. The model will include treatment as factor and 90% confidence intervals of the pairwise differences between treatment on the Ln scale will be calculated. The limits of the intervals will be back-transformed into exponential to obtain 90% confidence intervals of the ratios of geometric means between groups, on the original scale.

Safety analysis:

All safety data collected will be summarized and no inferential statistical tests are planned to be performed.

9.2 Sample size determination

9.2.1 Historical data

Sample size of this trial is based on an open-label Investigator Initiated Trial (IIT) for the treatment of early stage CTCL with resiquimod gel (Rook et al, 2015). The IIT showed approximately 58%-75% overall response rates on mCAILS for resiquimod 0.06% and/or 0.03% concentrations after one cycle (Week 12). No placebo arm was included in this trial. However, the results of a Phase 3 placebo controlled trial for Peldesine (BCX-34) cream as topical therapy for cutaneous T-cell lymphoma (Duvic et al, 2001 (a)) allowed to estimate the effect of a placebo. This trial appears to be well controlled, of sufficient duration (it includes 12 Weeks which is the primary time point of the present trial) and uses a similar endpoint (although not identical). The efficacy rate with placebo was approximately 20%.

9.2.2 Assumptions

Based on these historical data, this Phase 2 trial is powered using the following assumptions: 60% overall response rate on mCAILS at Week 12 with resiquimod gel versus 18% with placebo.

9.2.3 Sample size calculation

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 (28 subjects per treatment arm) subjects will be randomized.

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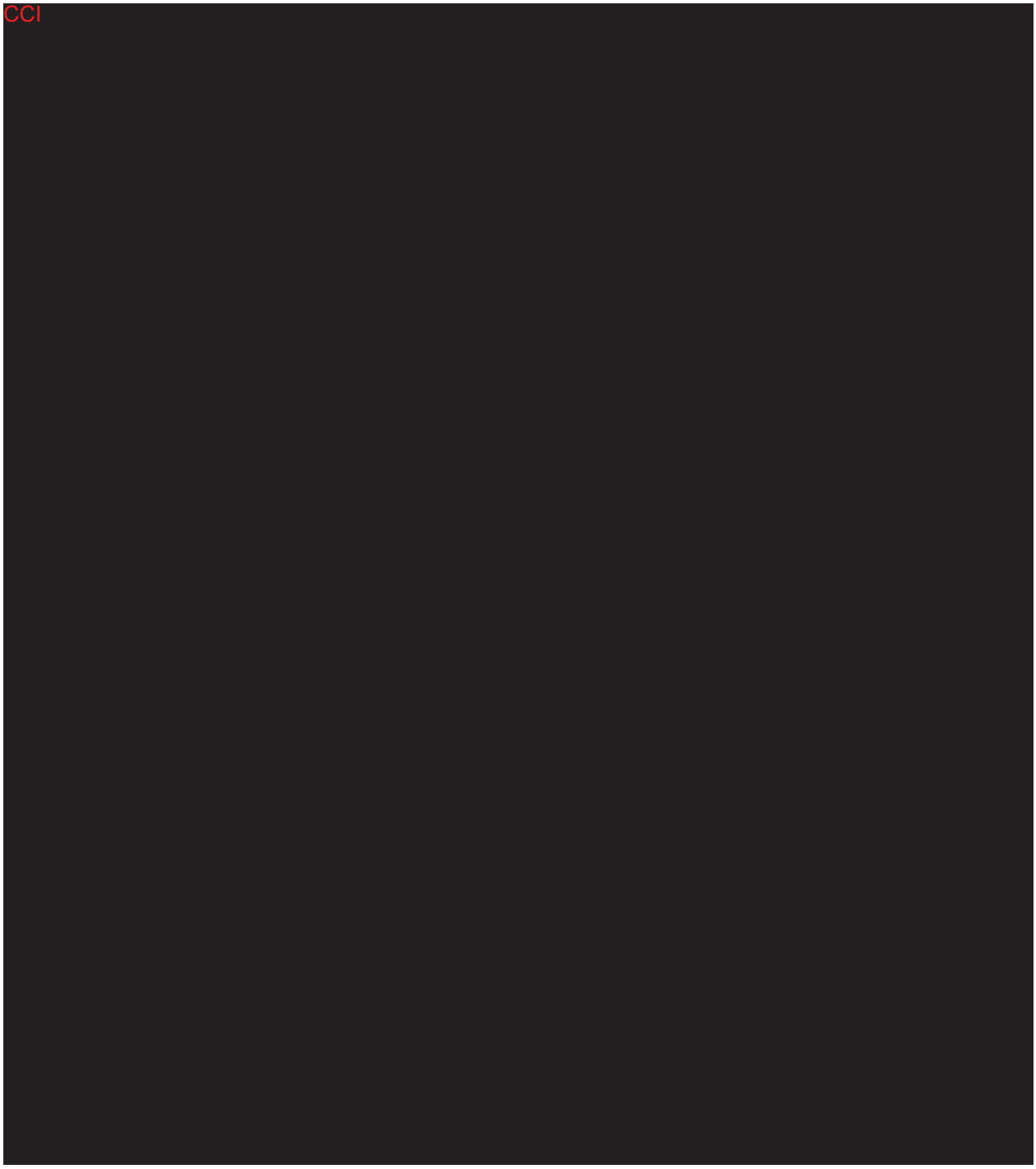

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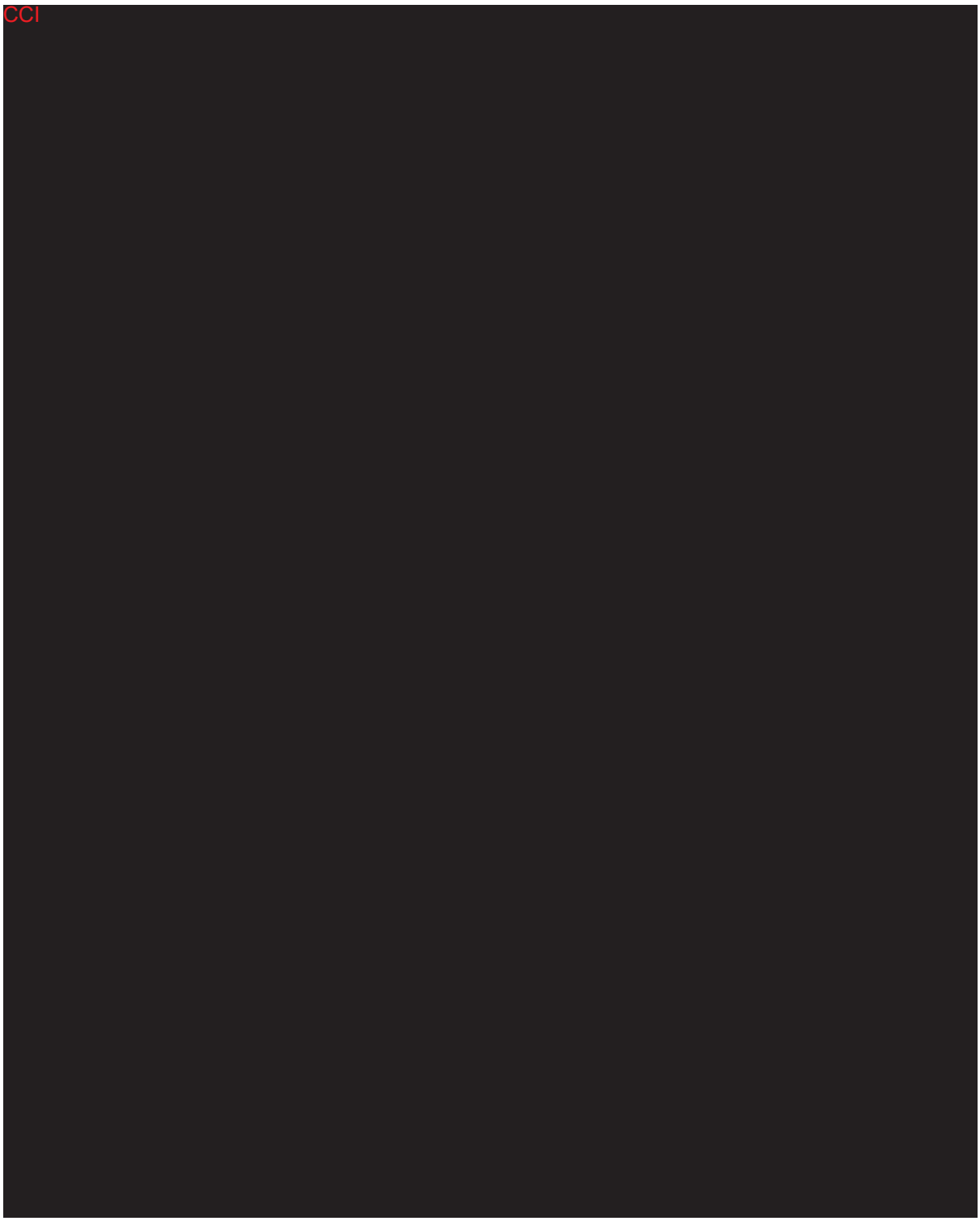

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13 APPENDICES

Appendix 1 Modified Composite Assessment of Index Lesion Severity (mCAILS)

Response of target lesion clinical signs will be assessed using the mCAILS score. The target lesions will be designated by the letter "X" and numbered in sequence, starting with 1X, 2X, 3X, 4X, and 5X. The target untreated lesion will be named "DIST". The location of all target lesions will be noted in the eCRF.

Individual target lesion clinical signs (erythema and scaling) will be graded using the scales found in Table 10 and Table 11 respectively. The greatest elevation of plaque within a given target lesion should be used in assessing the plaque elevation of that target lesion using Table 12. If pigmentation obscures all signs of possible erythema, then erythema should be recorded as grade 0. To determine the area of targeted lesions, the longest diameter and the longest diameter perpendicular to this diameter of each targeted lesion will be measured to the nearest millimeter. The lesion area will be the product of these two diameters and then graded as in Table 13.

If there is central clearing of a targeted lesion (clearing of disease within the outer boundaries of the lesion), then the product of the largest perpendicular diameters of the area(s) of clearing will be subtracted from the area determined from the outer boundary diameters before assigning the appropriate grade as in Table 13.

A mCAILS will be generated by a summation of the grades for each target lesion by erythema, scaling, plaque elevation, and lesion size (see Table 9).

Table 9 Modified Composite Assessment of Index Lesion Severity (mCAILS)

Clinical sign and degree or size (scale of 0-8 for signs, 0-3 for elevation, 0-18 for size)	Target lesions				
	1	2	3	4	5
Erythema					
Scaling					
Plaque elevation					
Lesion size					
Subtotal					
TOTAL (sum of subtotals)					

Table 10 The mCAILS scale of severity for target lesion signs and symptoms (erythema)

Scale	Grade
0	No evidence of erythema, possible brown hyperpigmentation
1	*
2	Mild: Light red lesion
3	*
4	Moderate: Red lesion
5	*
6	Severe: Very red lesion
7	*
8	Very severe: Extremely red lesion

* Intermediate intervals 1, 3, 5, and 7 serve as midpoints between the defined grades 0, 2, 4, 6, and 8.

Table 11 The mCAILS scale of severity for target lesion signs and symptoms (scaling)

Scale	Grade
0	No evidence of scaling on lesion
1	*
2	Mild: Mainly fine scales: lesion partially covered
3	*
4	Moderate: Somewhat coarser scales: lesion partially covered
5	*
6	Severe: Coarse thick scale; virtually all of the lesion covered
7	*
8	Very severe: Coarse, very thick scales, all of the lesions covered, very rough surface

* Intermediate intervals 1, 3, 5, and 7 serve as midpoints between the defined grades 0, 2, 4, 6, and 8.

Table 12 Plaque Elevation

Scale	Grade
0	No evidence of plaque above normal skin
1	Mild elevation
2	Moderate elevation
3	Marked elevation

Table 13 Target lesion size evaluation

Scale	Size of lesion (cm^2)
0	0 [no measurable area]
1	>0 and ≤4
2	>4 and ≤10
3	>10 and ≤16
4	>16 and ≤25
5	>25 and ≤35
6	>35 and ≤45
7	>45 and ≤55
8	>55 and ≤70
9	>70 and ≤90
10	>90 and ≤110
11	>110 and ≤130
12	>130 and ≤155
13	>155 and ≤180
14	>180 and ≤210
15	>210 and ≤240
16	>240 and ≤270
17	>270 and ≤300
18	>300

(Heald et al, 2003) (Olsen et al, 2011) (Duvic et al, 2001 (b))

Appendix 2 Modified Severity-Weighted Assessment Tool (mSWAT)

This technique involves the direct assessment of the body-surface area (BSA) of each type of lesion (palm plus fingers of the patient = approximately 1% BSA) in each of 12 areas of the body, multiplying the sum of the BSA of each lesion type by a weighting factor (patch = 1, plaque = 2, and tumor = 3 or 4) and generating a sum of the subtotals of each lesion subtype (Table 14).

Table 14 Modified Severity-Weighted Assessment Tool (mSWAT)

Body region	% BSA in body region	Assessment of involvment in subject's skin		
		Patch[a]	Plaque[b]	Tumor[c]
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		X1	X2	X4
Subtotal lesion BSA x weighting factor				

(a) Any size lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present.
(b) Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
(c) Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or ver ical growth.

mSWAT score equals summation of each column line.

Definitions in relation to skin involvement (mSWAT)

Complete Response:

100% clearance of skin lesions.

Partial Response:

50 to <100% clearance of skin disease from baseline without new tumors (T3) in subjects with T1, T2 or T4 only skin disease.

Stable Disease:

<25% increase to <50% clearance in skin disease from baseline without new tumors (T3) in subjects with T1, T2 or T4 only skin disease.

Progressive disease:

≥25% increase in skin disease ***from baseline*** based on mSWAT; There will be an exception to subjects with stage IA where ≥25% on mSWAT from baseline may not be clinically meaningful as long as the BSA affected with the disease is <10%;

OR

New tumors (T3) in subjects with T1, T2 or T4 only skin disease;

OR

Loss of response: In those with complete or partial response, increase of mSWAT score of greater than the sum of nadir plus 50% baseline score.
Nadir is defined as the lowest skin score (best response)

Relapse:

Any disease recurrence in those with complete response based upon baseline mSWAT.

(Olsen et al, 2011)

In case of progressive disease as defined above, subjects will discontinue the trial. Those with relapse, as defined above, will remain in the trial up to Week 36. Should the subject relapse between Week 36 to Week 72, the subject should be early terminated from the study.

Appendix 3 Skindex 29 Dermatology Survey of Quality of Life ©MMChren, 1996

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	❒	❒	❒	❒	❒
2. My skin condition affects how well I sleep	❒	❒	❒	❒	❒
3. I worry that my skin condition may be serious	❒	❒	❒	❒	❒
4. My skin condition makes it hard to work or do hobbies	❒	❒	❒	❒	❒
5. My skin condition affects my social life	❒	❒	❒	❒	❒
6. My skin condition makes me feel depressed	❒	❒	❒	❒	❒
7. My skin condition burns or stings	❒	❒	❒	❒	❒
8. I tend to stay at home because of my skin condition	❒	❒	❒	❒	❒
9. I worry about getting scars from my skin condition	❒	❒	❒	❒	❒
10. My skin itches	❒	❒	❒	❒	❒
11. My skin condition affects how close I can be with those I love	❒	❒	❒	❒	❒
12. I am ashamed of my skin condition	❒	❒	❒	❒	❒
13. I worry that my skin condition may get worse	❒	❒	❒	❒	❒
14. I tend to do things by myself because of my skin condition	❒	❒	❒	❒	❒
15. I am angry about my skin condition	❒	❒	❒	❒	❒

HOW OFTEN DURING THE PAST FOUR WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
16. Water bothers my skin condition (bathing, washing hands)	❒	❒	❒	❒	❒
17. My skin condition makes showing affection difficult	❒	❒	❒	❒	❒
18. I worry about side-effects from skin medications / treatments	❒	❒	❒	❒	❒
19. My skin is irritated	❒	❒	❒	❒	❒
20. My skin condition affects my interactions with others	❒	❒	❒	❒	❒
21. I am embarrassed by my skin condition	❒	❒	❒	❒	❒
22. My skin condition is a problem for the people I love	❒	❒	❒	❒	❒
23. I am frustrated by my skin condition	❒	❒	❒	❒	❒
24. My skin is sensitive	❒	❒	❒	❒	❒
25. My skin condition affects my desire to be with people	❒	❒	❒	❒	❒
26. I am humiliated by my skin condition	❒	❒	❒	❒	❒
27. My skin condition bleeds	❒	❒	❒	❒	❒
28. I am annoyed by my skin condition	❒	❒	❒	❒	❒
29. My skin condition interferes with my sex life	❒	❒	❒	❒	❒
30. My skin condition makes me tired	❒	❒	❒	❒	❒

Reference: https://eprovide.mapi-trust.org/instruments/skindex (website accessed on 07-June-2017)

Appendix 4 Patient Global Assessment of Improvement and Pruritus Numeric Rating Scale (NRS)

Table 15 Patient global assessment of improvement

1	Excellent improvement
2	Good improvement
3	Moderate improvement
4	No improvement
5	Worse

Table 16 Pruritus numeric rating scale (NRS)

For average itch intensity: “on a scale of 0 to 10, with 0 being ‘no itch’ and 10 being ‘worst imaginable itch’, how would you rate your itch overall during the previous 24 hours?”

No itch Worst imaginable itch

For maximum itch intensity: “on a scale of 0 to 10, with 0 being ‘no itch’ and 10 being ‘worst imaginable itch’, how would you rate your itch at the worst moment during the previous 24 hours?”

No itch Worst imaginable itch

Appendix 5 Summary of blood sample volumes

	Volume per timepoint	Screening	Cycle 1 (Baseline to Week 8)	Cycle 2 (Week 12 to Week 20)	Follow-up (Week 24 to Week 36)
Screening					
▪ Hematology	3+4.5 mL	7.5 mL			
▪ Biochemistry	6 mL	5 mL			
▪ Thyroid function	4 mL	4 mL			
▪ Serum pregnancy test	5 mL	5 mL			
TOTAL screening		21.5 mL			
Cycle 1 (Baseline to Week 8)					
▪ Hematology	3+4.5 mL		22.5 mL		
▪ Biochemistry	6 mL		18 mL		
▪ Thyroid function	4 mL		4 mL		
▪ PK sample (proof of exposure)	10 mL		20 mL		
▪ Immune cell dynamics – *select sites only*	5 mL		*10 mL*		
▪ Cellular immunology - *Optional*	30 mL		*90 mL*		
TOTAL Cycle 1			64.5 – 164.5 mL		
Cycle 2 (Week 12 to Week 20)					
▪ Hematology	3+4.5 mL			22.5 mL	
▪ Biochemistry	6 mL			18 mL	
▪ Thyroid function	4 mL			4 mL	
▪ PK sample (proof of exposure)	10 mL			40 mL	
▪ PK full assessment – *Optional*	10 mL			*240 mL*	
▪ Immune cell dynamics – *select sites only*	5 mL			*10 mL*	
▪ Cellular immunology - *Optional*	30 mL			*90 mL*	
TOTAL Cycle 2				94.6 – 424.5 mL	
Follow-up Period (Week 24 to Week 36)					
▪ Hematology	3+4.5 mL				15 mL
▪ Biochemistry	6 mL				12 mL
▪ Cellular immunology - *Optional*	30 mL				*30 mL*
TOTAL Follow-up period					27 – 57mL

Appendix 6 Examples of potent inhibitors and/or inducers of cytochrome P450 1A2 and 3A4

	Potent inhibitors	Potent inducers
CYP1A2	Ciprofloxacin Enoxacin Fluvoxamine Zafirlukast	-
CYP3A	Boceprevir Cobicistat Conivaptan Danoprevir and ritonavir Elvitegravir and ritonavir Grapefruit juice Indinavir and ritonavir Itraconazole Ketoconazole Lopinavir and ritonavir Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) Posaconazole Ritonavir Saquinavir and ritonavir Telaprevir Tipranavir and ritonavir Troleandomycin Voriconazole Clarithromycin Diltiazem Idelalisib Nefazodone Nelfinavir	Carbamazepine Enzalutamide Mitotane Phenytoin Rifampin St. John's wort

Note: Strong inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold. Strong inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80%.

This table is prepared to provide examples of clinical inhibitors / inducers and is not intended to be an exhaustive list.

Table adapted from:
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Drug-drug interactions data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].