TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A double-blind (sponsor unblinded) study to investigate safety, tolerability, pharmacokinetics, pharmacodynamics and clinical effect of repeat dosing of GSK2646264 in cutaneous lupus erythematosus patients

Compound Number: GSK2646264

Development Phase: I

Effective Date: 14-DEC-2017

Protocol Amendment Number: 03

Author (s):

PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N246677_00	2016-MAY-18	Original
2015N246677_01	2016-JUN-13	Amendment No. 1
Update to Time and Events Table Section 7.1.1 Group A and Section 7.1.3 Group B		
2015N246677_02	2016-JUN-21	Republished
There was an error regarding the phase of the study. It should be phase I, not phase III.		
2015N246677_03	2016-AUG-04	Amendment No. 2
Changes were required following a response from BfArM and ethics. Specifically, to clarify the dose of GSK2646264 applied; Clarification of which groups the inclusion/exclusion/withdrawal criteria apply to; Addition of an exclusion criteria related to subjects with SLE and/or significant disease in other organs; Clarification related to abnormalities observed and withdrawal of subjects who take prohibited medications; Addition of HIV test at screening; Addition of withdrawal criteria for Group A subjects receiving photoprovocation; Clarification of dose in UV exposure in photoprovocation		
2015N246677_04	2017-DEC-14	Amendment No. 3
Clarification of text in Objectives and Endpoints; Clarification of Treatment Groups with respect to LET patients and number of lesions they can present with; Update to number of patients to be recruited into each group; Update to Risk Assessment Table and Summary of Data/Mitigation Strategy; Alteration to Inclusion Criteria with respect to BMI; Inclusion of additional medication in Permitted Medications within Inclusion Criteria; Update to T&E table with respect to frequency of pregnancy testing for Group A and Group B; Revised Sample Size Considerations and Assumptions; Addition of in-stream review of data		

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14 DEC 2017

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): 2016-000277-20

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204860

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204860

1.1. Rationale

The autoimmune disease lupus erythematosus is associated with a broad range of cutaneous pathology which can be induced or exacerbated by exposure to sunlight. Key opinion leaders and patients have highlighted the need for a new and effective topical formulation, suitable for long term use on exposed areas, with a favourable safety and tolerability profile. GSK2646264 is a potent, selective small molecule inhibitor of spleen tyrosine kinase (SYK), a 72 kDa non-receptor tyrosine kinase, with suitable physical-chemical properties for dermal application. SYK mediates signalling through immuno-receptors notably the B-cell receptor (BCR), IgG receptors (FcγRI and III) and Fc epsilon receptors (FcεR1). Thus, SYK plays a crucial role in the regulation of immune responses, in both adaptive and innate immune recognition in a variety of cell types including macrophages, plasmacytoid dendritic cells, T and B cells. Initiation of the lesional inflammation in lupus erythematosus is thought to be driven through the activation of interferon (IFN) via the innate pathway. SYK mRNA is expressed in both subacute and chronic subtypes of lupus and is coexpressed with a large number of genes known to be stimulated by the IFN pathway. In addition, phosphorylation of the SYK protein is increased in CLE and expressed not only by infiltrating lymphocytes, but also by keratinocytes in inflamed areas. SYK inhibition *in vitro* with GSK143 a selective SYK inhibitor has been shown to inhibit production of key IFN responsive genes implicated in the lesional pro-inflammatory vicious circle in CLE [Liddle, 2011], [Braegelmann, 2016]. This study is designed to examine safety, tolerability, pharmacokinetics, pharmacodynamics and clinical effect of repeat dosing of GSK2646264 in patients with subacute and chronic CLE lesions and in acute CLE like lesions induced by photoprovocation (PV).

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of repeat doses of a cream formulation of GSK 2646264 in patients with CLE	• Safety and tolerability by laboratory tests, vital signs, 12-lead ECG, and AE reporting.
Secondary	
• To determine the effect of GSK2646264 on the reduction in clinical activity score from baseline in treated PV and existing CLE lesions • To evaluate the plasma concentrations of GSK2646264 in patients with CLE • To determine the effect of GSK2646264 on expression of IFN mRNA signature in skin biopsies in treated PV and existing CLE lesions	• Change from baseline of components of a modified RCLASI- composite clinical activity score at day 14 and day 28 in PV and existing lesions in erythema, oedema, dyspigmentation (and scaling in existing CLE lesions only) • PK parameters will be summarised • Change from baseline in IFN mRNA signature in skin biopsies at day 28 in PV and existing CLE lesions

Overall Design

This is a double blind (sponsor unblinded) Phase Ib two group study to investigate repeat doses of GSK2646264, a spleen tyrosine kinase (SYK) inhibitor administered via topical delivery, on safety, pharmacodynamic effect and clinical efficacy in active CLE lesions and in acute CLE like lesions induced by an established protocol of PV. The study population will be adult subjects (at least 18 years of age) that have been diagnosed with either subacute or chronic CLE.

Treatment Groups and Duration

Subjects with CLE that meet the entry criteria at the time of screening will be enrolled into two treatment arms dependent on the number of active lesions they present with.

Group A: Patients with fewer than 2 active lesions will be enrolled into group A and exposed to PV for 3 consecutive days. Patients with Lupus Erythematosus Tumidus (LET) can be enrolled into Group A only, and can present with any number of lesions, so long as the existing lesions are not in the areas designated for photoprovocation. Patients will be assessed for the development of lesions up to 14 days from the first PV. Patients that develop PV lesions at any time during this period, as determined by the local investigative team, will receive 1% strength GSK2646264 on 1 lesion and placebo on 1 lesion daily and either 1% strength GSK2646264 or placebo on an area of uninvolved skin, for skin PK of study drug, for 28 days.

Group B: Patients that have a minimum of 2 active existing CLE lesions as determined by the investigators will be enrolled into group B and have one lesion treated with 1% GSK2646264 and 1 lesion with placebo.

A completed patient will be defined as a subject who receives at least 25 days of study drug and completes the end of treatment biopsy (at day 28) and assessment. Thereafter patients will be followed for 28 days or until complete resolution of induced PV lesions, as determined by the investigator.

Type and Number of Subjects

The study population will be adults (at least 18 years of age). We aim to recruit approximately 25 patients into the study with the aim to randomise approximately 20 patients that have been evaluated by the investigators and diagnosed with subacute or chronic cutaneous lupus erythematosus. Approximately 10 patients will undergo PV in group A. PV response rates are estimated at 50% and we expect up to 5 PV positive patients to be randomised into the study. We aim to enroll approximately 15 patients into group B. We will include females of reproductive potential (FRP) in both groups of this study given the age and gender distribution (9:1-Female:Male preponderance) of the disease. Exclusion of FRP would significantly impair recruitment into the study and may affect the relevance of the data generated as the predominant patient population would be excluded.

Early termination of the study may occur due to feasibility of recruitment and/or individual subjects reaching safety stopping criteria.

Analysis

All data will be listed and summarised.

Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Change from baseline in each clinical activity assessment will be analysed by study part; part A will be summarised descriptively and part B will be analysed using a repeated measures mixed model including visit, treatment and lesion position as fixed effects and subject as a random effect. Estimates of the treatment means and differences will be presented with the associated 95% confidence intervals.

Change from baseline in each IFN mRNA signature endpoints will be analysed by study part; part A will be summarised descriptively and part B will be analysed using a mixed model including treatment and lesion position as fixed effects and subject as a random effect. Estimates of the treatment means and differences will be presented with the associated 95% confidence intervals. If the data is not normally distributed a transformation may be applied to the data.

Full details will be provided in the reporting and analysis plan.

In this sponsor-unblinded bilateral design study, 1 or more unblinded data reviews, using all available data to date, may be carried out by senior managers (not involved in the study conduct) and/or study team members (involved in the study conduct) to aid in portfolio and budget decisions. These administrative reviews will have no impact on the ongoing study. Full details will be provided in the reporting and analysis plan prior to the first administrative review.

2. INTRODUCTION

2.1. Study Rationale

GSK2646264 is a potent, selective small molecule inhibitor of SYK, a 72 kDa non-receptor tyrosine kinase, with suitable physical-chemical properties for dermal application being developed for once daily treatment of skin lesions in CLE.

SYK is an intracellular protein tyrosine kinase that is expressed in many cell types and involved in a variety of receptor-mediated signal-transduction pathways notably through the BCR, IgG receptors (FcγRI and III) and Fc epsilon receptors (FcεR1). Systemic administration of small-molecule inhibitors of SYK activity suppress a number of inflammatory disease models such as skin injury and kidney damage in MRL/lpr mice as well as established skin lesions in such mice. In addition, inhibition of SYK can result in the disappearance of established skin lesions in BAK–/–BAX–/– double-knockout mice, which spontaneously develop inflammatory skin lesions [Deng, 2010].

Initiation of the lesional inflammation in CLE is thought to be driven through the activation of IFN via the innate pathway. The expression pattern of IFN-inducible antiviral proteins (e.g. MxA) and chemokines (e.g. CXCL9, CXCL10) reflects the characteristic inflammatory pattern found in different subtypes of CLE and in acute CLE lesions induced by photoprovocation. SYK mRNA is expressed in both subacute and chronic subtypes of lupus and is co-expressed with a large number of genes, such as MxA and CXCL10, known to be stimulated by the IFN pathway [Braegelmann, 2016]. In addition, phosphorylated SYK protein is expressed not only by infiltrating lymphocytes, but also by keratinocytes in inflamed areas. SYK inhibition in vitro with the selective inhibitor GSK143 has been shown to inhibit the production of key IFN responsive genes implicated in the lesional pro-inflammatory vicious circle in CLE [Liddle, 2011], [Braegelmann, 2016]. These results have been confirmed by gene expression analysis of lesional discoid lupus erythematosus skin biopsies, revealing a strong “type I IFN mRNA signature” including expression of IFN-inducible genes, such as IRF1, MxA and others. Moreover, this data provided evidence that type I IFNs and potentially autoreactive cytotoxic lymphocytes targeting adnexal structures are associated with scarring CLE lesions and might be responsible for their disfiguring character.

2.2. Brief Background

The autoimmune disease lupus erythematosus predominantly affects FRP and is associated with a broad range of cutaneous pathology. Current topical treatments for CLE include tacrolimus, retinoid and steroid based regimes are only partially effective and limited in their use by long term side effects.

Key opinion leaders and patients have highlighted the need for a new and effective topical formulation, suitable for long term use on exposed areas, with a favourable safety and tolerability profile in comparison to topical steroids and immunosuppressants. In particular, a reduction in the extent of scarring caused by lesions in exposed areas such as the face and scalp is urgently required and would greatly impact on the quality of life (QoL) in patients with CLE.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of repeat doses of a cream formulation of GSK 2646264 in patients with CLE	• Safety and tolerability by laboratory tests, vital signs, 12-lead ECG, and AE reporting.
Secondary	
• To determine the effect of GSK2646264 on the reduction in clinical activity score from baseline in treated PV and existing CLE lesions	• Change from baseline of components of a modified RCLASI- composite clinical activity score at day 14 and day 28 in PV and existing lesions in erythema, oedema, dyspigmentation and (scaling in existing CLE lesions only)
• To evaluate the plasma concentrations of GSK2646264 in patients with CLE	• PK parameters will be summarised
• To determine the effect of GSK2646264 on expression of IFN mRNA signature in skin biopsies in treated PV and existing CLE lesions	• Change from baseline in IFN mRNA signature in skin biopsies at day 28 in PV and existing CLE lesions
Exploratory	
• To determine the effect of GSK2646264 on expression of IFN protein markers in skin biopsies in treated PV and existing CLE lesions	• Change from baseline in IFN proteins (eg MxA, CXCL10) in skin biopsies at day 28 in PV and existing CLE lesions
• To determine the effect of GSK2646264 on expression of pSYK and SYK protein in skin biopsies in treated PV and existing CLE lesions	• Change from baseline in pSYK and SYK protein in skin biopsies at day 28 in PV and existing CLE lesions
• To determine the effect of	• Change from baseline in immune cell

Objectives	Endpoints
GSK2646264 on immune cell markers in skin biopsies in treated PV and existing CLE lesions • To determine the effect of GSK2646264 on the histological disease activity in PV and existing CLE lesions • To evaluate the skin concentrations of GSK2646264 in patients with CLE	proteins (eg CD3, CD20, CD11c, CD123, CD68) in skin biopsies at day 28 in PV and existing CLE lesions • Change from baseline in histopathology score (including parakeratosis, ballooning/hydropic degeneration, epidermal cell-death, junctional and dermal inflammation) in skin biopsies at day 28 in PV and existing CLE lesions • Skin biopsy concentrations and derived pharmacokinetic parameters of GSK2646264

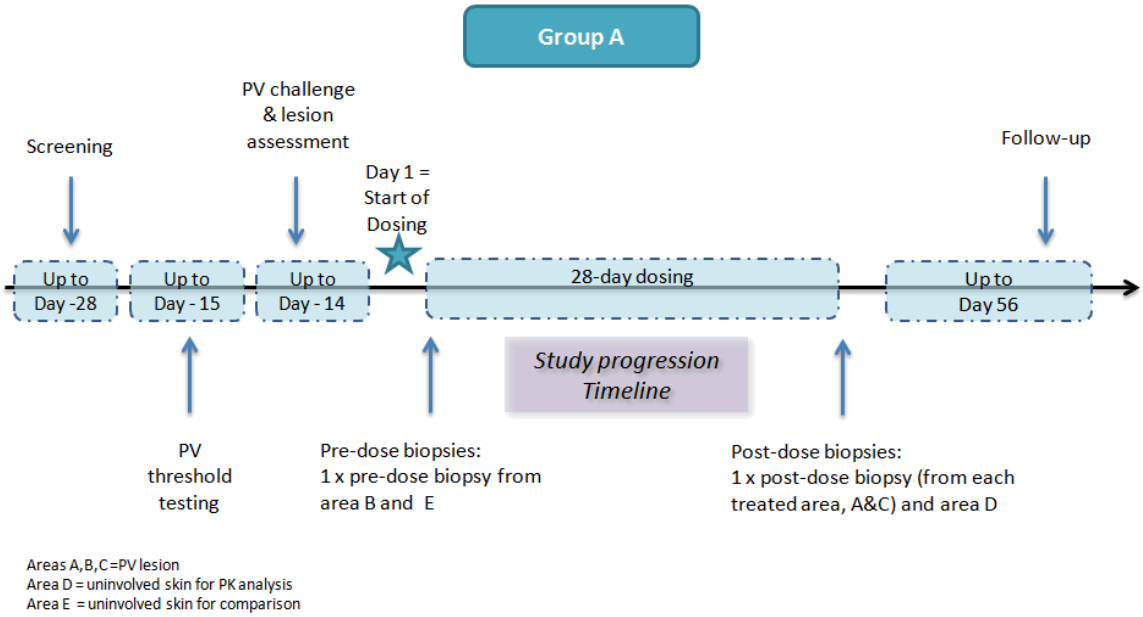
4. STUDY DESIGN

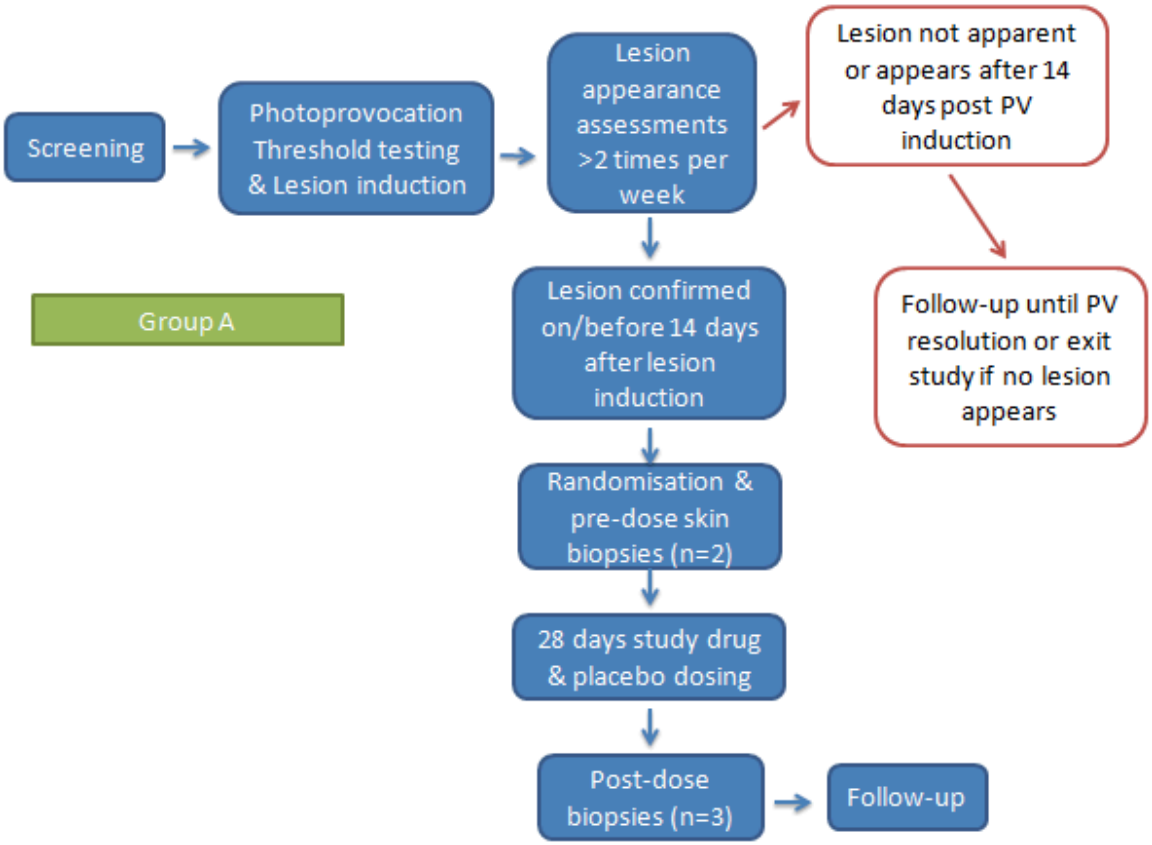
4.1. Overall Design

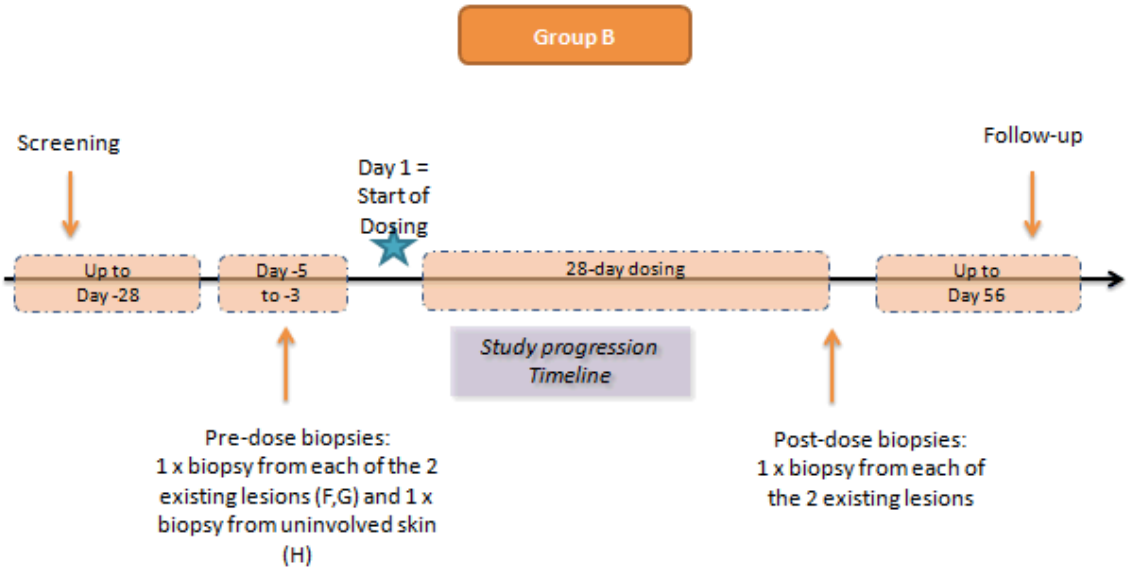
This is a double blind (sponsor unblinded) Phase Ib study to investigate repeat topical doses of GSK2646264 over 28 days on safety, pharmacodynamic effect, clinical efficacy and tolerability in active CLE and in lesions induced by a well established protocol of PV. The study population will be adult subjects (at least 18 years of age) that have been evaluated by the investigative site team and been diagnosed with either subacute or chronic CLE. Patients with Lupus Erythematosus Tumidus (LET) are allowed in group A only. The study has a 28 day maximum screening period and subjects who meet the entry criteria will be entered into one of two treatment groups dependent on the number of active lesions at the time of screening. Approximately 10 patients with fewer than 2 active lesions at the time of screening will be enrolled into group A and will undergo photo-testing followed by PV for up to 3 consecutive days on 3 (7cm by 5cm) areas on their back. Patients with LET can be enrolled into Group A only, and can present with any number of lesions, so long as the existing lesions are not in the areas designated for photoprovocation Patients will be assessed at least twice weekly for up to 14 days from the first day of PV. Up to 5 patients that develop PV lesions at all three sites at *any time* during this period, as determined by the local investigative team, will have a biopsy of one PV lesion (B) and one area of uninvolved skin (E) on their back close to the PV lesions (see Section 4.2 schematic and Figure 1 for visual representation). The two non-biopsied PV lesions (A,C) will be randomised to receive 1% GSK2646264 on one lesion and placebo on the other once daily for 28 days. A biopsy will be obtained post-treatment from each of these treated lesions. An additional separate area of uninvolved skin on the back (D) will be randomised 4:1 to receive either GSK2646264 or placebo and a biopsy on day 28 (post-dose) will be taken for skin pharmacokinetics assessment. Patients that have not developed PV lesions by day 14 (expected to be approximately 50% of the subjects), as determined by the investigative team, will not be included in the study. A small percentage of patients will develop PV lesions more than 14 days after PV (defined in this study as a ‘non-responder’) and these patients will not be included in the study but will be followed up until PV lesion resolution, as determined by the investigator (see Section 7.1.2).

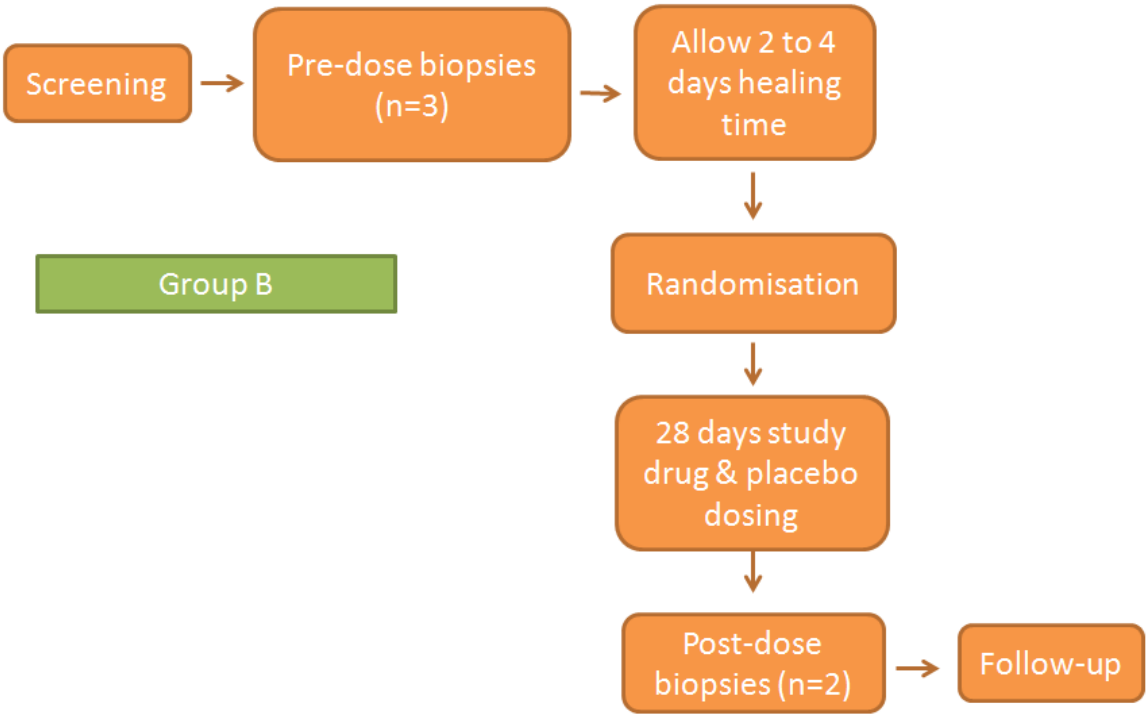
Group B will commence in parallel and recruit approximately 15 patients with a minimum of 2 active CLE lesions within the same anatomical area. At the day-5 to day -3 visit the two chosen lesions will be labelled based on size F (the larger) and G (the smaller). Pre-dose biopsies will be taken from both of the lesions (F+G) and an additional biopsy (H) from uninvolved skin from the same anatomical area will also be taken. The patients will be randomised 2-4 days later to allow for healing of the biopsies (F+G) and one lesion will then be treated with 1% GSK2646264 and the other with placebo once daily for 28 days. Biopsies will be obtained post-treatment from both treated CLE lesion (F+G). A completed patient will be defined as a patient who receives at least 25 days of study drug and completes the end of treatment biopsy (day 28) and assessment.

4.2. Study Overview Schematic




Screening
Photoprovocation Threshold testing & Lesion induction
Lesion appearance assessments >2 times per week
Lesion not apparent or appears after 14 days post PV induction
Follow-up until PV resolution or exit study if no lesion appears
Group A
Lesion confirmed on/before 14 days after lesion induction
Randomisation & pre-dose skin biopsies (n=2)
28 days study drug & placebo dosing
Post-dose biopsies (n=3)
Follow-up


Group B
Screening
Day 1 = Start of Dosing
Follow-up
Up to Day -28
Day -5 to -3
28-day dosing
Up to Day 56
Study progression Timeline
Pre-dose biopsies: 1 x biopsy from each of the 2 existing lesions (F,G) and 1 x biopsy from uninvolved skin (H)
Post-dose biopsies: 1 x biopsy from each of the 2 existing lesions



Treatment Groups and Duration

In group A subjects will receive both active treatment and placebo-to-match treatment which will be randomly assigned to 2 PV lesions (A+C). The skin site from which the biopsy to quantify concentration of drug in the skin in group A is taken (site D) will be randomised 4:1 to receive either active treatment or placebo.

All subjects in group B will receive both active treatment and placebo to match treatment which will be randomly assigned to the two chosen natural lesions (F+G).

The total duration of the study for group A is anticipated to be approximately 14 weeks, consisting of the following: Screening period (up-to 28 days); photoprovocation and lesion development (3 to 15 days); study treatment period (28 days); follow-up period (28 days) or until resolution of PV lesions (whichever is the latter).

The total duration for group B is anticipated to be approximately 12 weeks, consisting of the following: Screening period (up-to 28 days); biopsies followed by 2-4 day healing period; study treatment period (28 days); follow-up period (28 days).

The duration of study treatment will be 28 days of once-daily cream application to a defined skin lesion area not more than 0.5% body surface area (~90cm^2).

4.3. Type and Number of Subjects

We will recruit approximately 25 patients with CLE into the study with the aim to randomise approximately 20 patients. Based on past clinical experience approximately 50% of patients recruited into group A will develop PV lesions and up to 5 PV positive

patients will be randomised. We aim to randomise approximately 15 patients into group B of the study.

If subjects prematurely discontinue the study, additional replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

Early termination of the study may occur due to feasibility of recruitment and/or individual subjects reaching safety stopping criteria.

4.4. Design Justification

This study is designed to investigate repeat topical doses of 1% GSK2646264 over 28 days on clinical safety, tolerability, pharmacokinetics, efficacy and pharmacodynamic effect in CLE and in CLE like lesions induced by PV.

The study population will include approximately 20 evaluable subjects with subacute CLE (SCLE), chronic CLE (CCLE) including LET (group A only). In group A the study comprises of a 28 day treatment period and patients will be followed thereafter for 28 days or until resolution of induced PV lesions as determined by the investigators. Endpoint assessments will be conducted at the end of the 28 day treatment period. The provoked PV lesions offers the advantage to study acute CLE like lesions that exhibit the characteristic IFN signature of CLE lesions but show no features of chronicity and scarring.

In group B outcomes will be assessed in existing CLE lesions of patients with SCLE or CCLE but not LET which in the context of a chronic autoimmune disease represent multiple stages of lesion development and activity and are heterogenous in nature.

The study is designed to deliver data on safety and tolerability and will inform future studies.

4.5. Dose Justification

GSK2646264 will be administered topically as a cream at 1% (w/w) strength.The maximum topically applied dose to any subject at any time point will be 10mg/cm^2 of cream over 90 cm^2 (maximum of ~0.5% Body Surface Area as determined by Du Bois, 1916). This equates to a maximum of 900mg of cream and therefore 9 mg of GSK2646264. A corresponding placebo will also be applied. Cream will be weighed both before and after application.

In part A of the first time in human study in healthy subjects (study 200196, NCT02424799, GlaxoSmithKline Document Number 2013N167482) GSK2646264 was given for up to 4 days as a cream of 1% strength (w/w) covering 5.2% BSA for 2 days followed by 10.2% BSA for 2 days. Preliminary data from the FTIH study suggests that GSK2646264 penetrates through the skin and reaches the systemic circulation.

A Population pharmacokinetics model was developed using clinical data from study 200196 part A (N=17 healthy volunteers) and 3 cold urticaria subjects from part B. This model predicted, for GSK2646264 administered topically as a cream of 1% strength (w/w) on 0.5% of BSA, a Cmax of 0.780 ng/mL and an AUC (0-24) at steady state of

17.2. ng.h/mL. Those exposures are well within safety margins as described in the Investigator Brochure and supplement [GlaxoSmithKline Document Number 2013N182566_02, GlaxoSmithKline Document Number 2015N268236_01 (Supplement 1) and GlaxoSmithKline Document Number 2016N281634_00 (Supplement 2]

Preclinically, when GSK2646264 was administered into *ex-vivo* human healthy skin *via* a microdialysis tube a dose-dependent inhibition of IgE-stimulated histamine release from dermal mast cells was observed. The concentration of GSK2646264 required to inhibit 90% histamine release in anti IgE-stimulated skin *ex vivo* is achievable by the topical route when administered at the 1% strength see GSK2646264 Investigator Brochure.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2646264 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Pregnancy & Lactation	Fetal malformations were seen after IV dosing to pregnant Dutch belted rabbits with a NOAEL that is expected to exceed the highest expected human exposure by 13 and 214 fold cover compared to the predicted AUC (220 ng.hr/mL) and Cmax (167 ng/ml) respectively at the NOAEL. In a subsequent study in the New Zealand White rabbits, neither cardiovascular nor skeletal abnormalities were detected by any route and dose at maternal plasma exposures similar to or higher than exposures achieved in Dutch Belted rabbit. Based on these new fetal and TK data, the abnormalities in the Dutch Belted rabbit study were unlikely to be test article-related because no fetal abnormalities were detected in the New Zealand White rabbit with a similar C_{max} (bolus route compared) or at a 4.5-fold higher AUC (bolus vs 24-hr continuous infusion compared). The higher number of specific cardiovascular and skeletal abnormalities observed in the Dutch Belted rabbit Embryofoetal Development (EFD) study is likely related to the known higher spontaneous background incidence of these findings in Dutch Belted relative to New Zealand White fetal rabbits based on Test Facility	Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. Female subjects of reproductive potential will undergo regular pregnancy testing (at screening, Day 1, Day 14, and at follow-up) and treatment will be stopped immediately if a subject is found to be pregnant during the study, see Section 7.1 for exact timings. Subjects will also be required to be using an appropriate contraceptive (failure rate <1%) prior to the start and during the study as outlined in the protocol Section 5.1, Inclusion criteria. Females of reproductive potential must be on established contraceptives 28 days before dosing begins.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	historical control data and this is also supported in literature (Posobiec, 2016) No similar changes were seen in the rat after substantially higher exposure. There is no data available on the effect of GSK2646264 in pregnancy and lactation in humans.	
Thyroid follicular epithelial hypertrophy	Minimal thyroid follicular epithelial hypertrophy was observed in all doses following iv administration of GSK2646264 in rats for 4 weeks. Thyroid hormones (TSH, T3 and T4) at a single timepoint 12 hours post last dose were within normal range. No similar changes were seen following dermal administration of GSK2646264 in rats for 4 weeks which resulted in similar AUC values but lower Cmax values. The ongoing clinical study has not identified clinical signs or symptoms of thyroid dysfunction to date.	The risk of thyroid effect in this study is considered not to be significant. Subjects with history of Graves' disease, thyroid cancer, or abnormal thyroid function as measured by TSH, free T4 and free T3, will be excluded from this study. Monitoring will be based on signs and symptoms, and serum markers of thyroid function will be measured in patients as outlined in Section 7.1

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hypersensitivity to formulation	Dose related dermal findings in the rat were limited to observations of transient erythema and eschar at 1 and 3% (w/w). Desquamation was observed in one control and one treated animal at 3% (w/w). There were no histopathological correlates to these observations. Erythema was also a transient observation in the minipig but occurred with both vehicle and test article formulations without relationship to GSK2646264 (mesylate salt) dose strength and without histopathological correlate. There may be potential for hypersensitivity reactions from the procedures used in the study or if subjects are allergic to ingredients in the study medications. The ongoing FTIH study has not identified any significant safety concerns to date, as assessed by adverse events.	Subjects will be excluded from the study if they are allergic to any ingredient of the study medications. Subjects will undergo regular medical assessment and instructed on what action to take in the event of an allergic reaction, see Section 7.1.
Study Procedures		
UV exposure	Risk for development of skin cancer	PV has been widely used in a number of multicenter trials with several thousand patients enrolled to date which show no evidence for enhanced skin cancer risk. The risk is further mitigated by strictly controlled exposure to UV on approximately 105cm^2 BSA [Kuhn, 2011].

4.6.2. Benefit Assessment

This study contributes to the development of medicines in an area of unmet need. Key opinion leaders and patients have highlighted the need for a new and effective topical formulation, suitable for long term use on exposed areas, with a favourable safety and tolerability profile in comparison to topical steroids and immunosuppressants. In particular, a reduction in the extent of scarring caused by lesions in exposed areas such as the face and scalp is urgently required and would greatly impact on the QoL in patients with CLE.

All patients in group B of the study will receive study drug on at least one CLE skin lesion for up to 28 days. This may improve the treated lesion and may have minor short term benefit in terms of appearance of the lesion and associated itch and pain.

4.6.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to mitigate the risk of patients taking part in this study, the associated risks are justified by the anticipated long term benefit to patients with CLE.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator Brochure [GlaxoSmithKline Document Number: 2013N182566_02, GlaxoSmithKline Document Number 2015N268236_01 (Supplement 1) and GlaxoSmithKline Document Number 2016N281634_00 (Supplement 2)]

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential. All inclusion/exclusion criteria and withdrawal criteria apply to subjects in both Part A and Part B, unless specifically stated otherwise.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Between 18 and 70 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Subject values for the following parameters TSH, free T4, and free T3 within the normal range. 3. Subject has confirmed diagnosis of LET (group A only), subacute or chronic CLE as determined by the investigators. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included: only if the investigator in consultation with the Medical Monitor if required agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

WEIGHT
4. Body mass index (BMI) $\geq$19kg/m^2 (inclusive)

SEX
5. Male OR Female **Females**: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy • Documented Bilateral Oophorectomy • Postmenopausal defined as 12 months of spontaneous amenorrhea. In questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be

required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 12.4) from 28 days prior to the first dose of study medication and until 12 days after the last dose of study medication and completion of the follow-up visit.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
6. Capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

RELEVANT HABITS
7. All subjects must be free from scarring or skin markings (e.g. tattoos or piercings) and open wounds on the defined areas of the body that cream will be applied onto or that will be exposed to PV, unless in the opinion of the investigator it will not compromise the subjects' safety and quality of data. 8. Able to refrain from exposure to extended and direct sunlight during the study period, from screening until follow up, especially the area that is under treatment during the study. 9. Able to refrain from using self-tanning products on the areas on which the study cream will be applied for the duration of the study from screening to follow-up. 10. Able to refrain from shaving and waxing the areas on which the study cream will be applied during the duration of the study from screening to follow up.

PERMITTED MEDICATIONS
11. Patient stable on either no treatment or on : • **Corticosteroids** (≤7.5mg/day prednisone or prednisone equivalent or less) for a minimum of 30 days prior to screening and through to Day 28. • and /or **hydroxychloroquine** (≤400mg daily dose) for a minimum of 60 days prior to the initial photoprovocation for group A or Randomisation Visit for group B through to day 28. • **Topical steroids** applied to the defined areas of the body that are not exposed to photoprovocation or study cream from screening to Day 28. • **Topical calcineurin inhibitors and retinoids** applied to the defined areas of the body that are not exposed to photoprovocation or study cream from screening to Day 28. • **Opioids, if required for acute and chronic pain management, and documented in the medical history/records**

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTC INTERVAL)
1. ALT >2xULN; 2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) 3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 4. QTcF > 450 msec, or QTcF > 480 msec in subjects with Bundle Branch Block NOTES: • The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. • The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. • For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP). 5. History of any past or present benign or malignant skin conditions and disease, unless in the opinion of the investigator it will not compromise the subjects safety and quality of data. 6. Subjects with active Systemic Lupus Erythematosus (SLE) and/or significant disease in any other organ than the skin, as judged by the Investigator after discussion with the medical monitor 7. Subjects with a history of Graves disease 8. Subjects with a history of thyroid cancer. 9. Unable to refrain from vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half lives (whichever is longer) prior to the screening visit until the completion of the follow-up assessments, unless in the opinion of the Investigator, in consultation with the GSK Medical Monitor if required, the medication will not interfere with the study procedures or compromise subject safety. 10. Clinically significant abnormality in the hematological, clinical chemistry, or urinalysis screen, that in the opinion of the investigator after discussion with the

medical monitor, requires further investigation, medical intervention or poses a safety risk to the subject to participate in the trial.

11. Subjects who start prohibited medications or therapies at any time during the study will be withdrawn from the study.

    The following medications and therapies are prohibited at any time during the study:

    - Use of other investigational agents (biologic or non-biologic; investigational applies to any drug not approved for sale in the country in which it is used).
    - Co-enrolment into another study of an investigational agent or non-drug therapy.
    - Use of biological agents (e.g., alemtuzumab, rituximab, ATG) during the clinical study or within 12 months to first dose of study treatment.
    - Use of other immunosuppressive drugs commonly used in SLE including Azathioprine, Methotrexate, Mycophenolate, Cyclophosphamide within 3 months to first dose of study treatment.

RELEVANT HABITS
12. History of regular alcohol consumption within 3 months of the study defined as: Alcohol will be allowed but limited to an average weekly intake of <21 units for males or <14 units for females). 13. Direct exposure to UV light (e.g. sunbathing) to the testing areas within 2 weeks of study entry.

CONTRAINDICATIONS
14. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation (refer to the Investigator Brochure for a list of excipients).

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
15. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. 16. A positive HIV test at screening 17. A positive pre-study drug screen. 18. Where participation in the study would result in donation of blood or blood products in excess of 450 ml within 3 months. 19. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current

study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

20. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

Country Specific Exclusion criteria wording for Germany:

21. Subjects that are employees of either GlaxoSmithKline (sponsor) or one of the study centres (investigators).
22. Subjects who live in detention on court order or on regulatory action, see §40 subsection 1 sentence 3 no. 4 AMG. (Arzneimittelgesetz).

CONCOMITANT MEDICATIONS

23. Oral Prednisolone

- Greater than 7.5 mg by mouth daily.
- Any increase in dose from screening to Day 28

24. Hydroxychloroquine

- Greater than 400mg oral daily.
- Any increase in dose from screening to Day 28.

25. Photosensitizing drugs within 5 half-lives prior to the photoprovocation visit.

5.3. Screening/Baseline Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.6).

Screening assessments that yield initially abberant results (e.g. safety laboratory samples) may be repeated by the investigator based on their judgement. Subject re-screening is allowed up to a maximum of 2 times.

5.4. Withdrawal/Stopping Criteria

WITHDRAWAL CRITERIA(Specific for Group A ONLY)
1. A subject will be withdrawn from the study, if they demonstrate an excessive or adverse reaction to the photoprovocation, as judged by the Investigator after discussion with the medical monitor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. In case a subject withdraws from study they should be encouraged to continue contraception for 28 days.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

At the time a subject withdraws, every effort should be made to conduct assessments stipulated at the follow-up visit, as per the time & events tables, Section 7.1.

If subjects prematurely discontinue the study, additional replacement subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator.

5.4.1. Safety Related Stopping Criteria for an Individual Subject

A female subject will be withdrawn form the study if a positive pregnancy test is obtained during the study.

A subject may be withdrawn from the study if they present dose limiting toxicity.

Toxicity is defined as dose-limiting toxicity if it meets the following criteria:

- Occurs within 24 hours after any dose.

- and is considered by the Investigator to be possibly or probably related to treatment

- and, for AE or laboratory abnormality, is severe
- and, for tolerability,
    - is of Grade 3 or higher for "dermal response scoring (i)", and
    - is Grade C, F, G, or H according to the "other effects scoring (ii)" (Section 5.4.2 below)
- and for Thyroid function – TSH to remain within the normal range at Day 14

If dose limiting toxicity is observed in an individual, the investigator or designee may use their medical judgment to stop dosing the individual subject, and is required to immediately inform the GSK medical monitor or designee. They will then decide whether it is necessary for the Safety Review Team (SRT: See Section 10.8) to be convened immediately for review of the data and decision on dose adjustment or withdrawal of the individual subject.

The SRT will:

- Evaluate and confirm potential dose-limiting toxicities both as data is generated (so-called 'in-stream review'), and at any point during the study when a bulk of data review is determined necessary (e.g. this may be conducted once all subjects in group A complete all study visits, or at any other point during study conduct).
- Pause enrolment and/or request safety-related changes to the trial protocol.

At a minimum (but not limited to), the following data-sets will be reviewed by the SRT:

- Clinical laboratory assessments
- Vital signs
- Adverse (& serious adverse) Events
- Local tolerability assessments

Additional data-sets not listed above may also be reviewed as deemed appropriate by the SRT.

A subject may be withdrawn from the study if they present a Serious Adverse Event (SAE), regardless of its severity, and reasonably attributable in the opinion of the investigator to dosing with GSK2646264.

A subject will be withdrawn if they require concomitant medications as specified and listed in Section 5.2.

In the presence of any of the above events, every effort will be made to take a blood sample at the time of the event for pharmacokinetics analysis.

5.4.2. Local Tolerability

Tolerability will be assessed with the following skin irritation scoring system, where the score consists of a numeric score according to the dermal response scoring i), and a letter according to the other effects scoring ii), as follows:

i) Dermal response scoring:

0 = no evidence of irritation

1 = minimal erythema, barely perceptible (pink)

2 = moderate erythema (definite redness), readily visible; minimal edema or minimal papular response

3 = strong erythema (intense redness), or erythema and papules

4 = definite edema

5 = erythema, edema, and papules

6 = vesicular eruption

7 = strong reaction spreading beyond test site

ii) Other effects:

Z = no other effect

A = slight glazed appearance

B = marked glazing

C = glazing with peeling and cracking

F = glazing with fissures

G = film of dried serous exudate covering all or part of the dose site

H = small petechial erosions and/or scabs

5.4.3. Safety Related Study Specific Dose Adjustment Criteria

If AEs are of severe intensity and are similar across subjects, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK2646264, or if dose limiting toxicity (see Section 5.4.1), are observed in at least 2 subjects, relevant reporting and discussion with the GSK medical monitor and the SRT will take place.

If a Serious Adverse Event (SAE) occurs in 1 subject and is deemed to be drug related, this would be deemed an SAR (Serious Adverse Reaction), and dosing will be halted in the individual (Relevant reporting and discussion with the GSK medical monitor and the SRT will take place, and halting of dosing will be considered for all study subjects). If dosing is halted for the entire study, any resumption of dosing will only take place after consideration by the SRT and discussion with the investigators and may necessitate approval of a substantial amendment submitted to the Ethics committees and Regulatory authorities.

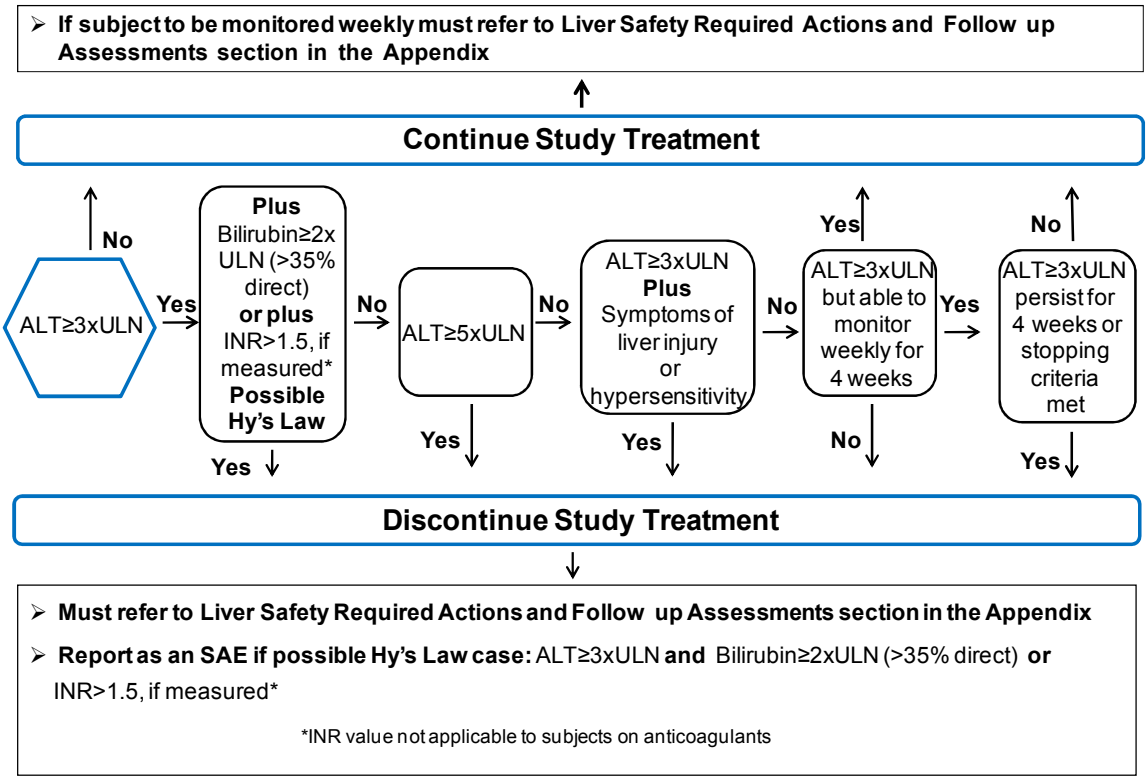
If average predicted or observed C_{max} or AUC(0-24 h after last dose) of GSK264624 is greater than 16 ng/mL or 220 ng.hr/mL, respectively, subsequent doses may be adjusted based on toxicology cover and this will be agreed by the SRT.

5.4.4. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.2.

5.4.4.1. Study Treatment Restart or Rechallenge

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval is granted
- Ethics and/or IRB approval is obtained, if required, and

- Separate consent for treatment restart/rechallenge is signed by the subject

Refer to Section 12.2 for full guidance.

5.4.5. QTc Stopping Criteria

A subject that meets either criterion below will be withdrawn from the study. The same QT correction formula (e.g QTcF) should be used to determine inclusion and discontinuation for any individual subject throughout the study.

- QTcF > 500 msec,
- Change from baseline: QTcF >60 msec

If a subject has underlying bundle branch block the following withdrawal criteria should be used instead:

Baseline QTcF value (with underlying bundle branch block)	**QTcF withdrawal criteria**
<450 msec	>500 msec
450-480 msec	≥530 msec

Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTcF values of the 3 ECGs to determine whether the subject should be discontinued from the study.

5.5. Subject and Study Completion

A completed subject will be defined as a subject who receives at least 25 days of study drug and completes the end of treatment biopsy and assessment. Patients will be followed as per the Time & Events table, Section 7.1 until complete resolution of induced PV lesions.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment	
Product name:	1% GSK2646264	Placebo
Formulation description:	White to off white aqueous cream	White to off white aqueous cream
Dosage form:	Topical	Topical
Unit dose strength(s)/Dosage level(s):	1% (w/w)	NA
Route/ Administration/ Duration:	Topical	Topical
Dosing instructions:	Should be applied topically as directed.	Should be applied topically as directed.
Physical description:	White-to-off-white aqueous cream stored in amber glass jars	White-to-off-white aqueous cream stored in amber glass jars
Manufacturer/ source of procurement:	Medpharm Guildford	Medpharm Guildford

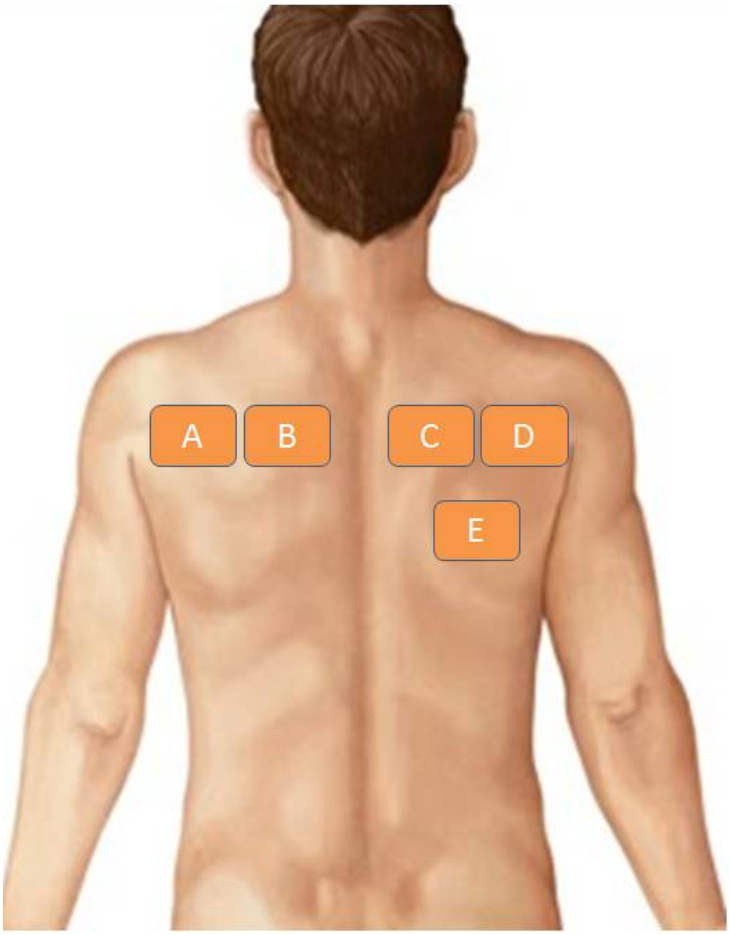
6.1. Treatment Assignment

Subjects will be assigned to treatment in accordance with the randomisation schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Skin areas A-C in group A are horizontally distributed across the back of the patient. The PV lesions will be labelled A, B, C. Study drug and placebo will be randomly assigned to lesions A and C. Lesion B will not be assigned a treatment and will be used for the baseline skin biopsy. A further area of uninvolved skin (area D) will also be treated with study drug or placebo in a ratio of 4:1. Another area of uninvolved skin (area E) will not be treated with either study drug or placebo and will be used solely to take a baseline biopsy.

Lesion/Skin Area	Type	Biopsy timing	Receives Drug/Placebo
A	PV lesion	Day 28	✓
B	PV lesion	Baseline	
C	PV lesion	Day 28	✓
D	Uninvolved Skin	Day 28	✓
E	Uninvolved Skin	Baseline	

Figure 1 Approximate anatomical representation of UV lesion induction sites (A-C) and uninvolved skin (D and E) for Group A



Group A subjects will be assigned to the following regimens:

	Skin Sites A/C/D	Assignment ratio
Sequence 1	A/P/A	4
Sequence 2	A/P/P	1
Sequence 3	P/A/A	4
Sequence 4	P/A/P	1

P=Placebo, A= GSK2646264 1%

The nurse administering the treatments may be aware whether a patient is assigned to sequences 1/4 or sequences 2/3, however they will remain blinded to treatment.

In group B, at the day -5 to day -3 visit, prior to pre-dose biopsies being taken, the two chosen lesions will be labelled F and G based on size (F >G). The two lesions will be randomly assigned placebo or study drug. An area of uninvolved skin (area H) will not

be treated with either study drug or placebo and will be used solely to take a biopsy at baseline. These lesions can be on any part of the body (all 3 lesions must be in the same anatomical area), but the subject must consent to be biopsied from the area with the lesions.

Lesion/Skin Area	Skin Type	Biopsy timing	Receives Drug/Placebo
F	Natural lesion	Baseline and Day 28	✓
G	Natural lesion	Baseline and Day 28	✓
H	Uninvolved Skin	Baseline	

Group B subjects will be assigned to one of the following regimens:

	Skin Sites F/ G	Assignment ratio
Sequence 1	A/P	1
Sequence 2	P/A	1

P=Placebo, A= GSK2646264 1%

6.2. Blinding

This will be a double blind (sponsor unblinded) study and the following will apply.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF

A subject may continue in the study if that subject's treatment assignment is unblinded.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.3. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

6.4. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of GSK2646264 is given below. More details will be available for sites to use in the Study Reference Manual (SRM).

- Only subjects enrolled in the study may receive study treatment and only authorized site staff, which may include a study nurse, may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff which may include a study nurse.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff which may include a study nurse. Adequate precautions to avoid direct eye or skin contact should be taken. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.5. Compliance with Study Treatment Administration

When subjects are dosed at the site or at their home, they will receive study treatment directly from the investigator or designee which may include a study nurse. The date and time of each dose administered in the clinic or at the subjects home will be recorded in the source documents.

6.6. Treatment of Study Treatment Overdose

For this study, any dose of GSK2646264 that is above the intended dose is considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator or physician in charge of the subject at the time will use clinical judgment to treat any overdose.

6.7. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because the indication being studied is not life threatening or seriously debilitating and/or other treatment options are available.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition, whether or not GSK is providing specific post-study treatment.

6.8. Lifestyle and/or Dietary Restrictions

6.8.1. Contraception Requirements

Contraception requirements are presented in detail in Section 12.4

6.8.2. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication until after the final dose.

6.8.3. Caffeine, Alcohol, and Tobacco

- Alcohol will be allowed but limited to an average weekly intake of <21 units for males or <14 units for females).
- There are no caffeine or tobacco restrictions.

6.8.4. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies.

Subjects should refrain from taking part in water based activities such as swimming and use of sauna/steam room for up to 3 hours following application of the study drug.

Showers/bathing should not be taken up to 3 hours following application of the study drug.

Use of sunscreen (UVA/UVB protection cream) on any PV lesions or lesions treated with study drug or placebo should be avoided.

6.9. Concomitant Medications and Non-Drug Therapies

6.9.1. Permitted Medications and Non-Drug Therapies

See Section 5.1 for complete details of permitted medications.

6.9.2. Prohibited Medications and Non-Drug Therapies

See Section 5.2 for complete details of prohibited medications

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws.

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or others] assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 450 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- Photographs may be taken of some of the procedures, tests, medical condition or reactions which may occur during the study.

7.1. Time and Events Tables

7.1.1. Group A

Procedure	Screening (up to Day -28)	Day -15	Day -14	Day -13 to -1	Day 1	Day 2 to Day 13	Day 14	Day 15 to Day 20	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up[a]	[a] All procedures listed to also be conducted if a subject decides to prematurely withdraw/discontinue
Informed Consent	X												
Inc/Exc criteria assessment	X												
Demography	X												
Pregnancy Test (women)	X				X		X					X	Pregnancy testing to be performed at Screening, on Day 1 (pre-dose), Day 14 (pre-dose) and once during follow-up, with day recorded
TSH, free T4, free T3	X				X		X					X	
Vital Signs	X	X			X		X			X			
Safety Lab Samples (clin chem, haematol, Urinalysis)	X	X		X	X		X			X		X	On days of dosing samples should be taken predose. Sample timepoints during the Day-13 to Day-1 period are as follows: – once weekly during visits to assess PV lesion development
Full Physical Exam	X											X	

Procedure	Screening (up to Day -28)	Day -15	Day -14	Day -13 to -1	Day 1	Day 2 to Day 13	Day 14	Day 15 to Day 20	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up[a]	[a] All procedures listed to also be conducted if a subject decides to prematurely withdraw/discontinue
Brief Physical Exam				X									Assessment to be performed pre-dose Sample timepoints during the Day-13 to Day-1 period are as follows: – once weekly during visits to assess PV lesion development
12-lead ECG	X				X		X					X	On days of dosing assessments should be performed predose
SLE clinical assessment	X				X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose .
ANA, anti-dsDNA , anti-Ro and anti-La antibodies, HIV, Hep B, Hep C, FSH, Drug screen	X												
Skin Biopsies					X[b]					X[b]			[b]Day 1 biopsies will be taken pre-dose. Day 28 biopsies will be taken 4 hours post-dose
UV threshold testing		X											
Photoprovocation			X[c, d]										Performed 24 hours after UV threshold testing. [c]PV occurs once every 24 hours for 3 days on Day-14, Day-13 & Day-12. [d] If PV induced lesions appear at all 3 sites after Day -14 or Day -13, PV treatment can be stopped early

Procedure	**Screening (up to Day -28)**	**Day -15**	**Day -14**	**Day -13 to -1**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up[a]**	[a] All procedures listed to also be conducted if a subject decides to prematurely withdraw/discontinue
Lesion induction assessment			<- ----X------>										
Lesion resolution assessment											X	X	
Clinical score					X		X			X			Components of the RCLASI as defined in Section 7.3 Assessments to be performed pre-dose
Local Tolerability Assessment					X	X	X	X	X	X	X		Assessments to be performed pre-dose and up to one hour following dosing on days of dosing
Dosing					X	X	X	X	X	X			Once daily
Randomisation					X								Pre-dose

Procedure	**Screening (up to Day -28)**	**Day -15**	**Day -14**	**Day -13 to -1**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up[a]**	[a] All procedures listed to also be conducted if a subject decides to prematurely withdraw/discontinue
PK blood sample					X	X	X		X	X	X	X	Sampling timepoints: Day 1 = pre-dose; and 5hrs (±1 hr) Between Day 2 and Day13: one pre-dose sample or postdose sample with time recorded since last dose Day 14: predose sample Between Day 21 and Day27: one pre-dose sample or postdose sample with time recorded since last dose Day 28: one postdose sample with time recorded since last dose Between Day 29 and Day 42: one sample with time recorded since last dose Follow-up visit: one sample with sampling day recorded
AE/SAE Review	X	<----------X---------->											
Concomitant Medication Review	X	<----------X---------->											

7.1.2. Group A PV non-responders

Procedure	Once-weekly up to 28 days after first photoprovocation	Final Follow-up visit(s) (occurs until final PV induced lesion has resolved)	Notes
Brief Physical Exam	X	X	IMPORTANT: This table is **ONLY** applicable for subjects in group A that do not develop PV induced lesions within 14 days of the start of photoprovocation Once-weekly assessments will occur from 15 days post first photoprovocation up until 28 days post first photoprovocation. Any PV lesion that develops after 15 days post-photoprovocation will be followed up until resolution.
PV Lesion assessment (if present)	X	X	
AE/SAE Review	X	X	
Concomitant Medication Review	X		

7.1.3. Group B

Procedure	**Screening (up to Day -28)**	**Day -5 to -3**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up (between Day 43 to Day 56)[a]**	[a] All procedures listed to also be conducted if a subject decides to prematurely withdraw/discontinue
Informed Consent	X										
Inc/Exc criteria assessment	X										
Demography	X										
Pregnancy Test (women)	X		X		X					X	Pregnancy testing to be performed at Screening, on Day 1 (pre-dose), Day 14 (pre-dose) and once during follow-up, with day recorded
TSH, free T4, freeT3	X		X		X					X	
Vital Signs	X	X			X			X			
Safety Lab Samples (clin chem ,haematol, Urinalysis)	X	X	X		X			x		X	On days of dosing samples should be taken predose
Full Physical Exam	X									X	
Brief Physical Exam			X								Assessment to be performed pre-dose
12-lead ECG	X		X		X					X	On days of dosing assessments should be performed predose
SLE clinical assessment	X		X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose .
ANA, anti-dsDNA antibodies, anti-Ro and anti-La antibodies, HIV, Hep B, Hep C, FSH, Drug screen	X										
Lesion selection		X									Refer to Section 4.1 and

Procedure	**Screening (up to Day -28)**	**Day -5 to -3**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up (between Day 43 to Day 56)[a]**	[a] All procedures listed to also be conducted if a subject decides to prematurely withdraw/discontinue
											Section 6.1
Skin Biopsies		X[b]						X[b]			[b]2 to 4 days healing time will be allowed prior to randomisation and the first dose. Day 28 biopsies will be taken 4 hours post-dose
Clinical score			X		X			X			
Local tolerability Assessment			X	X	X	X	X	X	X		Assessments to be performed pre-dose and up to one hour following dosing on days of dosing
Dosing			X	X	X	X	X	X			Once daily
Randomisation			X								Pre-dose

Procedure	**Screening (up to Day -28)**	**Day -5 to -3**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up (between Day 43 to Day 56)[a]**	[a] All procedures listed to also be conducted if a subject decides to prematurely withdraw/discontinue
PK blood sample			X	X	X		X	X	X	X	Sampling timepoints: Day 1 = pre-dose; and 5hrs (±1 hr) Between Day 2 and Day13: one pre-dose sample or postdose sample with time recorded since last dose Day 14: predose sample Between Day 21 and Day27: one pre-dose sample or postdose sample with time recorded since last dose Day 28:one postdose sample with time recorded since last dose Between Day 29 and Day 42: one sample with time recorded since last dose Follow-up visit: one sample with sampling day recorded
AE/SAE Review	X										
Concomitant Medication Review	X										
Lesion resolution assessment									X	X	

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The SLE clinical assessment is an assessment defined by the investigator as per usual practice at their site and is used to determine predominant skin disease and no evidence of life or organ threatening systemic features.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity. In addition, smoking & alcohol history will be recorded.

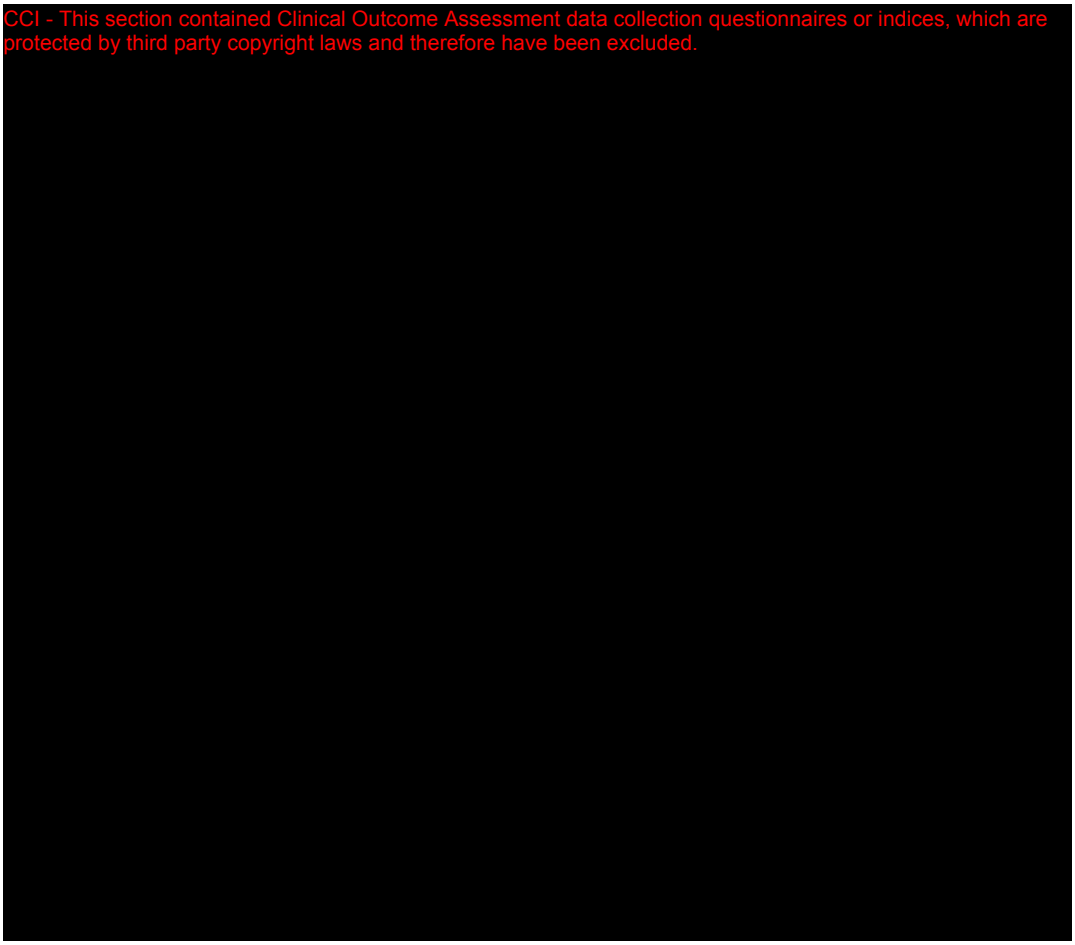
Procedures conducted as part of the subject's routine clinical treatment and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

7.3. RCLASI (Clinical Score)

The RCLASI (Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index) will be used to assess disease activity. RCLASI has been previously described by [Kuhn, 2010] as reliable in a multi-centre clinical trial setting for evaluation of CLE disease activity and damage to the skin in CLE sub-types.

In this study, components of the RCLASI will be utilised: only activity and dyspigmentation part of the damage scores will be recorded for lesions. All other sections in the RCLASI (site of involvement, mucous membrane lesions, and alopecia will not be used for clinical activity score).

Figure 2 RCLASI sub-section



7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests [(such as vital signs, physical exams and laboratory safety tests)] may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Section 12.3.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.3 Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 12.3) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

7.4.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in subjects with CLE or SLE and can be serious/life threatening:

- Exacerbation of SLE or transformation of CLE into SLE with organ involvement other than the skin

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a SAE). These events will be recorded on the DRE page in the subject's CRF within the appropriate time frame *agreed upon by the SRT* for completion of DRE CRF pages. These DREs will be monitored by the SRT (see Section 10.8) on a routine basis.

NOTE: However, if either of the following conditions apply, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject, or*
- *The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product*

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Pregnancy

Any female subject who becomes pregnant while participating

- will discontinue study medication immediately.
- Please refer to Section 12.4.1 for details of collection of pregnancy information

7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Skin, Cardiovascular, Respiratory, Renal, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.4.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate.
- Three readings of blood pressure and pulse rate will be taken
- First reading should be rejected
- Second and third readings should be averaged to give the measurement to be recorded in the CRF.

7.4.5. Electrocardiogram (ECG)

- Triplicate 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.5 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

7.4.6. Photo-provocation model

Subjects will undergo UV threshold testing on six 4.5 cm^2 areas of the lower back each for UVA and UVB irradiation during screening. The maximum UVA irradiation received will be 100 Jcm^{-2} and the maximum UVB will be 200 $mJcm^{-2}$ as per the method described by Kuhn, *(2011)*. Twenty four hours after day 1 threshold testing, the MTD (minimal tanning dose; the lowest dose causing persistent pigment darkening evaluated 24 hours after irradiation) for UVA and the MED (minimal erythema dose) for UVB will be evaluated. The dose intensities used for UVA and UVB irradiation for photoprovocation will be customized for each subject by determining his or her individual MTD and MED evaluated 24 hours after threshold testing. Thereafter, three 7x5 cm areas of uninvolved skin on the upper back will be irradiated daily for 3 consecutive days with the MTD for UVA followed by 1.5 MEDs of UVB. All subjects

will be prohibited from exposure to direct UV radiation and the use of sunscreen on the tested areas.

7.4.7. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 1, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Q^2 laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 1.

Table 1 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Drug screen (to include at minimum: amphetamines, barbiturates,			

Laboratory Assessments	Parameters
	cocaine, opiates, cannabinoids and benzodiazepines) • Serum or urine hCG Pregnancy test (as needed for women of child bearing potential) • Free T3 • Free T4 • TSH • ANA, Anti-ds DNA, Anti-Ro and Anti-La antibodies
NOTES : 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.4 and Appendix 2.	

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of GSK2646264 will be collected at the time points indicated in Section 7.1, Time and Events Tables. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Approximately 3 mL of blood will be collected into a blood collection tube at time points indicated in Section 7.1.

Detailed sample collection, processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.5.2. Biopsy Sample Collection

Skin punch biopsies, 4 mm in size, will be taken from subjects as detailed in the SRM at the timepoints indicated in Section 7.1 Time and Events Table. Biopsies will always be taken after the relevant clinical assessments have been completed.

Biopsies for drug concentration and disposition analysis of GSK2646264 will be collected from subjects in group A only. One biopsy will be obtained at day 28 from uninvolved skin (skin area D), treated with either study drug or placebo.

The actual date and time of each skin biopsy sample collection will be recorded. Results will be reported under a separate Bioimaging protocol.

Details of PK skin biopsy sample processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.5.3. Sample Analysis

Plasma analysis will be performed under the control of PTS-IVIVT-BIB/TPR/NCGOM, GlaxoSmithKline,the details of which will be included in the Study Reference Manual (SRM). Concentrations of GSK2646264 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Skin biopsy analysis will be performed under the control of Bioimaging, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK2646264 will be determined in skin biopsies using currently approved bioanalytical methodology. Drug disposition will be investigated using Matrix Assisted Laser Desorption Ionization-Imaging Mass Specrometry (MALDI-IMS), as samples permit. Skin biopsy analysis will be completed under a separate protocol and results will be reported separately. Once the plasma or skin biopsies have been analyzed for GSK2646264 any remaining plasma or skin biopsy may be analyzed for other compound-related metabolites and the results reported under a separate Mechanistic Safety & Disposition/Scinovo, GlaxoSmithKline protocol.

7.6. Biomarker(s)/Pharmacodynamic Markers

7.6.1. Biomarker(s)/Pharmacodynamic measurements in Skin Biopsies

For group A, two pre-dose biomarker / PD biopsies will be obtained at day 1, one from an uninvolved skin region on the back of the patient (skin area E), and one from PV lesion B. At day 28, post-treatment biomarker / PD biopsies will be obtained from the two remaining non-biopsied PV lesions A and C, one PV lesion treated with study drug and one PV lesion treated with placebo.

For group B, three pre-dose biomarker / PD biopsies will be obtained at day -5 to -3, one from an uninvolved skin region (H) and from both of the existing lesions F and G. Ideally, the uninvolved skin region biopsy should be located on the same anatomical body area close to the existing lesion biopsy. At day 28, post-treatment biomarker / PD biopsies will be obtained from both of the existing lesions F and G, one existing lesion treated with study drug and one lesion treated with placebo.

Details of biomarker / PD skin biopsy sample processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

Biomarker / PD biopsies will be evaluated histologically and by transcriptomic analysis.

Transcriptomic analysis will determine the effect of placebo and active treatment on IFN gene expression. Gene expression will be measured using microarray technology, and/or

alternative equivalent technologies, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for a skin biopsy sample. Genes may include but are not restricted to: MX1, MX2, OAS1, OAS2, IFI44. The same samples may also be used to confirm findings by application of alternative technologies.

Histological assessments of the biopsies will explore changes in pharmacodynamic and disease biomarkers. Markers may include (but are not restricted to):

IFN proteins (such as MxA) to assess changes in IFN signalling

SYK protein levels (such as but not restricted to phospho-SYK and total SYK) to assess target engagement

Immune cell and immune cell marker expression (such as CD3+ T cells, CD20+ B cells, CD11c+ myeloid dendritic cells and CD68+ macrophages).

Pathological evaluation for general appearance using a histopathological disease activity score, scoring on parakeratosis, ballooning, necrosis, junctional inflammation and the extent of dermal infiltrate.

7.6.2. Novel Biomarkers

With the subject's consent, the same skin biopsy samples described in Section 7.6.1 may be used for the purposes of measuring novel biomarkers to identify factors that may influence CLE, and/or medically related conditions, as well as the biological and clinical responses to GSK2646264. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with CLE or medically related conditions and/or the action of GSK2646264 may be identified by application of transcriptomic and /or histological analysis of skin biopsy samples.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

8. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objectives of the study are to evaluate the safety and tolerability of repeat doses of a cream formulation of GSK2646264 in patients with CLE . No formal statistical comparisons will be conducted to assess these objectives. If deemed appropriate to assess key efficacy and pharamacodynamic endpoints, the following exploratory comparisons may be conducted :

- GSK2646264 treatment vs. Placebo in PV lesions
- GSK2646264 treatment vs. Placebo in natural lesions

9.2. Sample Size Considerations

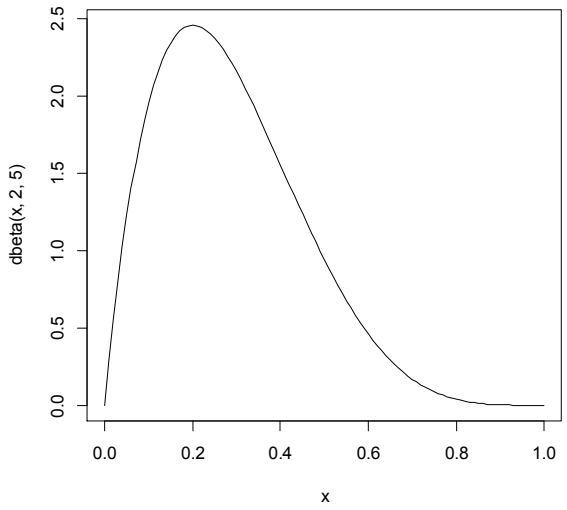
There are no formal calculations of power or sample size for this study. The sample sizes have been chosen based on feasibility, to primarily allow the assessment of safety and tolerability of GSK2646264 in patients with CLE.
We will recruit approximately 25 patients with CLE into the study with the aim to randomise approximately 20 patients. Approximately 10 patients will undergo PV in group A. PV response rates are estimated at 50% and we expect up to 5 PV positive patients to be randomised into the study. We aim to randomise approximately 15 patients into group B of the study. All patients will be treated with both GSK2646264 and placebo on separate lesions (see Section 6.1 for details).

9.2.1. Sample Size Assumptions

There are no formal calculations of power or sample size for this study. The sample sizes have been chosen based on feasibility.

The primary objective of the study is safety, where a number of safety events are of interest.

For group A, Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe 1 safety event in 5 then the posterior distribution would be Beta (2, 5), as outlined below:



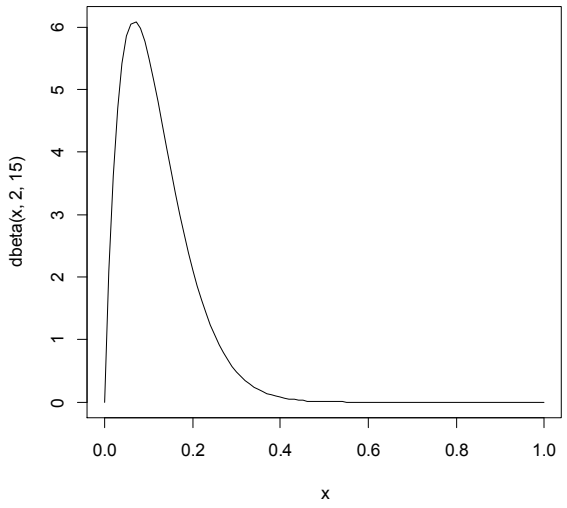
Where we can be 95% certain that the true probability of the safety event lies between 0.04 and 0.64.

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates with 5 subjects in part A. Additionally, if the number of subjects is lower than 5 in group A, then the true incidence rates of safety events that could not be ruled out would change.

These changes are outlined in the table below:

N completing the study	**Number of particular safety events observed with active**	**Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out**
5	0	46%
5	2	78%
4	0	52%
4	1	72%
4	2	85%

For group B, using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe 1 safety event in 15 then the posterior distribution would be Beta (2, 15), as outlined below:



Where we can be 95% certain that the true probability of the safety event lies between 0.02 and 0.30.

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates with 15 subjects in part B. Additionally, if the number of subjects is lower than 15 in group B, then the true incidence rates of safety events that could not be ruled out would change.

These changes are outlined in the table below:

N completing the study	**Number of particular safety events observed with active**	**Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out**
15	0	21%
15	2	38%
12	0	25%
12	1	36%
12	2	45%

9.2.2. Sample Size Re-estimation or Adjustment

A sample re-estimation is not planned for this study.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Safety Population: The safety Population is defined as subjects who receive at least one dose of study medication. This population is used for the summary of all data including safety, efficacy and pharmacodynamic (PD) data but excluding PK data.

Pharmacokinetic Population: The 'PK Population' is defined as subjects in the 'Safety' population who received an active dose and for whom a pharmacokinetic sample was obtained and analysed. This population is used for the summary of PK data only.

9.3.2. Interim Analysis

In this sponsor-unblinded bilateral design study, 1 or more unblinded data reviews, using all available data to date, may be carried out by senior managers (not involved in the study conduct) and/or study team members (involved in the study conduct) to aid in portfolio and budget decisions. These administrative reviews will have no impact on the ongoing study. Full details will be provided in the reporting and analysis plan prior to the first administrative review.

9.4. Key Elements of Analysis Plan

Data will be summarized and analysed according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP.

Final analysis of groups A and B will be reported together after all subjects in groups A (up to 5 subjects) and B (approximately 15 subjects) have completed their follow-up visit.

9.4.1. Primary Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

9.4.2. Secondary Analyses

All plasma GSK2646264 concentration data will be graphically represented, descriptively summarised and listed appropriately. Plasma GSK2646264 concentration time data will be analysed using a population pharmacokinetics (PK) model developed previously using data from study 200196 (FTIH of GSK2646264). Population PK parameters (Cmax, AUC(0- τ) and terminal phase half life (t1/2) will be reported. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Descriptive statistics of both raw and change from baseline, where appropriate, (i.e. n, arithmetic mean, standard deviation, minimum, median and maximum) will be calculated

for erythema, oedema, dyspigmentation (and scaling in existing lesions only) and modified RCLASI and summarized study part. All data will be listed.

Change from baseline in each clinical activity assessment will be analysed for each lesion type using a mixed effects model fitting visit, treatment and lesion location as fixed effects and subject as random. Estimates of the differences between GSK2646264 and placebo will be calculated and appropriate statistical inferences based on these results will be made.
Descriptive statistics of both raw and change from baseline data, where appropriate, (i.e. n, arithmetic mean, standard deviation, minimum, median and maximum) will be calculated for the IFN mRNA endpoints and summarized by lesion type (PV and natural lesions). All data will be listed.

If data permits, formal statistical analyses of the IFN mRNA endpoints may be conducted.

Change from baseline in each IFN mRNA signature endpoints will be analyzed by study part using a mixed model including treatment and lesion number as fixed effects and subject as a random effect. Estimates of the treatment means and differences will be presented with the associated 95% confidence intervals. Distributional assumptions underlying the analyses will be assessed as appropriate. If these assumptions are strongly violated, appropriate transformations will be investigated and if required alternative statistical analyses considered.

Full details will be provided in the RAP.

9.4.3. Exploratory Analyses

Descriptive statistics of both raw and change from baseline data, where appropriate, (i.e. n, arithmetic mean, standard deviation, minimum, median and maximum) will be calculated for the exploratory pharmacodynamic endpoints and summarized by study part. All data will be listed.

If data permits, formal statistical analyses of the exploratory pharmacodynamic endpoints may be conducted, if deemed appropriate and full details will be provided in the RAP. Based on the specified statistical analyses, estimates of the differences between GSK2646264 and placebo will be calculated and appropriate statistical inferences based on these results will be made. Distributional assumptions underlying the analyses will be assessed as appropriate. If these assumptions are strongly violated, appropriate transformations will be investigated and if required alternative statistical analyses considered.

Full details of the reporting of exploratory endpoints will be provided in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the

investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.8. Safety Reivew Team (SRT)

Instream review of unblinded safety data including AE, SAEs, vital signs and laboratory data will be conducted by a SRT during the study conduct. The membership of the SRT (including members of the central GSK study team) and the proposed frequency of review will be documented in the SRT charter.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
BMI	Body Mass Index
BCR	B-cell receptor
CCLE	Chronic Cutaneous Lupus Erythematosus
CLE	Cutaneous Lupus Erythematosus
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CV	Cardio Vascular
EFD	Embryofoetal development
FcεR1	Fc epsilon receptors
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTIH	First Time in Human
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HIV	Human Immuno-Deficiency Virus
HRT	Hormone Replacement Therapy
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IFN	Interferon
IRB	Institutional Review Board
LET	Lupus Erythematosus Tumidus
MALDI-MS	Matrix Assisted Laser Desorption Ionization-Imaging Mass Specrometry
mRNA	Messenger-Ribonucleaic Acid
MSDS	Material Safety Data Sheet
NOAEL	No Observed Adverse Effect Level
PD	Pre-dose
PK	Pharmacokinetics
pSYK	Phosporylated- Spleen Tyrosine Kinase
PV	Photoprovocation
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QoL	Quality of Life
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SCLE	Sub-acute Cutaneous Lupus Erythematosus

SD	Standard Deviation
SLE	Systemic Lupus Erythematosus
SRM	Study Reference Manual
SRT	Safety Review Team
SYK	Spleen Tyrosine Kinase

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Liver Safety – Study Treatment Restart

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted • **If restart/rechallenge not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>**	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained within 24 hours after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy	
ALT 3xULN and <5xULN and bilirubin <2xULN, without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the

investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Section 12.2 for the required liver chemistry follow-up instructions

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.3.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. • Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study. • Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer. • The use of a single question from a multidimensional health survey to designate a

cause-effect relationship to an AE is inappropriate.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory

reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via PIMS

• Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the Medical Monitor:
  • SAE listing
  • Demographic listing
  • Study treatment listing
• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
• If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the Medical Monitor. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.4. Appendix 4: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, with combined estrogen and progestogen [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011].
- Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Oral Contraceptive, either combined or progestogen alone Injectable progestogen [Hatcher, 2011]
    - Contraceptive vaginal ring [Hatcher, 2011]
    - Percutaneous contraceptive patches [Hatcher, 2011]

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2) 2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.4.1. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 48 hours of learning of a subject's pregnancy.

- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.3.6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- will discontinue study medication immediately.

12.5. Appendix 5 - Country Specific Requirements

No country-specific requirements exist.

12.6. Appendix 6 Protocol Changes

12.6.1. Protocol changes for Amendment 3 from the Amendment 2

Where the Amendment Applies

Amendment 3 applied to all sites

Summary of Amendment Changes with Rationale

Changes have been made to clarify the treatment groups with respect to LET patients, update the number of patients to be recruited into each group, update the risk assessment table, alter the inclusion criteria with respect to BMI and permitted medications, update the T&E table with respect to frequency of pregnancy testing, revise the sample size considerations and assumptions, and removal of the interim analysis.

List of Specific Changes

Title Page, Authors

Rationale for change: Author list was updated with new authors

REVISED TEXT:

PPD

Objectives and Endpoints

Rationale for Change: Clarification of CLE versus PV lesions

REVISED TEXT:

- To determine the effect of GSK2646264 on the histological disease activity in PV and existing **CLE** lesions

Section 1 Treatment Groups and Duration

Rationale for Change: Clarification of the number of lesions a patient can present with, and to allow LET patients with more than 1 lesion to enter the study

REVISED TEXT:

Subjects with CLE that meet the entry criteria at the time of screening will be enrolled into two treatment arms dependent on ~~whether they have a minimum~~ **the number of** ~~2~~ active lesions **they present with.**

Group A: Patients with fewer than ~~two~~2 active lesions will be enrolled into group A and exposed to PV for 3 consecutive days. **Patients with Lupus Erythematosus Tumidus (LET) can be enrolled into Group A only, and can present with any number of**

lesions, so long as the existing lesions are not in the areas designated for photoprovocation.

Section 1 Type and Number of Subjects

Rationale for Change: To amend the total number of subjects to be recruited into the study, and incorporate that termination may occur due to feasibility of recruitment of subjects reaching stopping criteria

REVISED TEXT

The study population will be adults (at least 18 years of age). We aim to recruit approximately ~~50~~**25** patients into the study with the aim to randomise ~~40~~ **approximately 20** patients that have been evaluated by the investigators and diagnosed with subacute or chronic cutaneous lupus erythematosus. Approximately ~~20~~**10** patients will undergo PV in group A. PV response rates are estimated at 50% and we expect ~~10~~**up to** 5 PV positive patients to be randomised into the study. We aim to enroll ~~up to 30~~ **approximately 15** patients into group B. We will include females of reproductive potential (FRP) in both groups of this study given the age and gender distribution (9:1-Female:Male preponderance) of the disease. Exclusion of FRP would significantly impair recruitment into the study and may affect the relevance of the data generated as the predominant patient population would be excluded.

Early termination of the study may occur due to feasibility of recruitment and/or individual subjects reaching safety stopping criteria.

Section 1 Analysis

Rationale for Change: Clarification of statistical analysis to be performed on each group.

REVISED TEXT:

Change from baseline in each clinical activity assessment will be analysed by study part; **part A will be summarised descriptively and part B will be analysed** using a repeated measures mixed model including visit, treatment and lesion position as fixed effects and subject as a random effect. Estimates of the treatment means and differences will be presented with the associated 95% confidence intervals.

Change from baseline in each IFN mRNA signature endpoints will be analysed by study part; **part A will be summarised descriptively and part B will be analysed** using a mixed model including treatment and lesion position as fixed effects and subject as a random effect. Estimates of the treatment means and differences will be presented with the associated 95% confidence intervals. If the data is not normally distributed a transformation may be applied to the data.

In this sponsor-unblinded bilateral design study, 1 or more unblinded data reviews, using all available data to date, may be carried out by senior managers (not involved in the study conduct) and/or study team members (involved in the study conduct) to aid in portfolio and budget decisions. These administrative reviews will have no

impact on the ongoing study. Full details will be provided in the reporting and analysis plan prior to the first administrative review.

Section 4.1 Overall Design

Rationale for Change: Clarification of number of lesions that LET patients in Group A can present with, and a change to the total number of subjects to be recruited to each group of the study.

REVISED TEXT:

….The study has a 28 day maximum screening period and subjects who meet the entry criteria will be entered into one of two treatment groups dependent on ~~whether they have a minimum~~**the number** of ~~2~~active ~~CLE~~ lesions ~~or not~~ at the time of screening. Approximately ~~20~~**10** patients with fewer than 2 active lesions at the time of screening will be enrolled into group A and will undergo photo-testing followed by PV for **up to** 3 consecutive days on 3 (7cm by 5cm) areas on their back. **Patients with LET can be enrolled into Group A only, and can present with any number of lesions, so long as the existing lesions are not in the areas designated for photoprovocation** Patients will be assessed at least twice weekly for up to 14 days from the first day of PV~~. Patients~~ **Up to 5** patients that develop PV lesions at all three sites at *any time* during this period, as determined by the local investigative team, will have a biopsy of one PV lesion (B) and one area of uninvolved skin (E) on their back close to the PV lesions (see Section 4.2 schematic and Figure 1 for visual representation)….

….Group B will commence in parallel and recruit ~~up to 30~~ **patients****approximately 15patients** with a minimum of 2 active CLE lesions within the same anatomical area~~(i.e. back, chest, head)~~…..

Section 4.3 Type and Number of Subjects

Rationale for Change: Amendment to number of subjects to be recruited into each group.

REVISED TEXT:

We will recruit approximately ~~50~~**25** patients with CLE into the study with the aim to randomise ~~40~~**approximately 20** patients. Based on past clinical experience approximately 50% of patients recruited into group A will develop PV lesions and ~~approximately 50%~~**up to 5 PV positive** patients will be ~~non-responders~~**randomised**. We aim to randomise ~~up to 30~~**approximately 15** patients into group B of the study.

Section 4.4 Design Justification

Rationale for Change: Amendment to number of subjects to be recruited into each group.

REVISED TEXT: The study population will include approximately **20**~~40~~ evaluable subjects with subacute CLE (SCLE), chronic CLE (CCLE) including LET (group A only).

Section 4.6.1 Risk Assessment

Rational for Change: Update to the Risk Assessment Table due to additional data

REVISED TEXT:

Summary of Data/Rationale for Risk	**Mitigation Strategy**
Fetal malformations were seen after IV dosing to pregnant **Dutch belted** rabbits with a NOAEL that is expected to exceed the highest expected human exposure by 13 and 214 fold cover compared to the predicted AUC (220 ng.hr/mL) and Cmax (167 ng/ml) respectively at the NOAEL. **In a subsequent study in the New Zealand White rabbits, neither cardiovascular nor skeletal abnormalities were detected by any route and dose at maternal plasma exposures similar to or higher than exposures achieved in Dutch Belted rabbit. Based on these new fetal and TK data, the abnormalities in the Dutch Belted rabbit study were unlikely to be test article-related because no fetal abnormalities were detected in the New Zealand White rabbit with a similar C_{max} (bolus route compared) or at a 4.5-fold higher AUC (bolus vs 24-hr continuous infusion compared). The higher number of specific cardiovascular and skeletal abnormalities observed in the Dutch Belted rabbit Embryofoetal Development (EFD) study is likely related to the known higher spontaneous background incidence of these findings in Dutch Belted relative to New Zealand White fetal rabbits based on Test Facility historical control data and this is also supported in literature (Posobiec, 2016)**	Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate. Female subjects of reproductive potential will undergo regular pregnancy testing **(at screening, Day 1, Day 14, and at follow-up)** and treatment will be stopped immediately if a subject is found to be pregnant during the study, see Section 7.1 for exact timings. Subjects will also be required to be using an appropriate contraceptive (failure rate <1%) prior to the start and during the study as outlined in the protocol Section 5.1, Inclusion criteria. Females of reproductive potential must be on established contraceptives 28 days before dosing begins.

Section 5.1 Inclusion Criteria

Rationale for Change: Broaden the inclusion criteria to allow greater range of BMI and use of certain medications if documented in medical history

REVISED TEXT:

~~Body weight ≥ 50 kg and~~ Body mass index (BMI) ~~within the range~~ **≥19.9** ~~– 35 kg/m2~~ (inclusive)

Opioids, if required for acute and chronic pain management, and documented in the medical history/records

Section 6.1 Treatment Assignment

Rationale for Change: Clarification of where the areas for treatment can be.

REVISED TEXT

These lesions can be on any part of the body (all 3 lesions must be in the same anatomical area), but the subject must consent to be biopsied from the area with the lesions

Section 7.1.1 Time and Events Table Group A

Rationale for Change: Alteration to the frequency of pregnancy testing required throughout

REVISED TEXT:

Procedure	**Screening (up to Day -28)**	**Day -15**	**Day -14**	**Day -13 to -1**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up[a]**	[a] All procedures listed ~~should~~ **to** also be conducted if a subject decides to prematurely withdraw/discontinue
Informed Consent	X												
Inc/Exc criteria assessment	X												
Demography	X												
Pregnancy Test (women)	X	~~X~~		~~X~~	X	~~X~~	X		~~X~~	~~x~~		X	Pregnancy testing ~~between Day 1 & Day 28 should be performed once every 7 days~~**. to be performed at Screening, on Day 1 (pre-dose), Day 14 (pre-dose) and once during follow-up, with day recorded**~~Pregnancy test on Day 1 will be pre-dose~~.

Procedure	**Screening (up to Day -28)**	**Day -15**	**Day -14**	**Day -13 to -1**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up[a]**	[a] All procedures listed ~~should~~ **to** also be conducted if a subject decides to prematurely withdraw/discontinue
TSH, free T4, free T3	X				X		X					X	
Vital Signs	X	X			X		X			X			
Safety Lab Samples (clin chem, haematol, Urinalysis)	X	X		X	X		X			X		X	On days of dosing samples should be taken predose. Sample timepoints during the Day-13 to Day-1 period are as follows: – once weekly during visits to assess PV lesion development
Full Physical Exam	X											X	
Brief Physical Exam				X									Assessment to be performed pre-dose Sample timepoints during the Day-13 to Day-1 period are as follows: – once weekly during visits to assess PV lesion development
12-lead ECG	X				X		X					X	On days of dosing assessments should be performed predose
SLE clinical assessment	X				X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose.
ANA, anti-dsDNA , anti-Ro and anti-La antibodies, HIV, Hep B, Hep C, FSH, Drug screen	X												

Procedure	**Screening (up to Day -28)**	**Day -15**	**Day -14**	**Day -13 to -1**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up[a]**	[a] All procedures listed ~~should~~ **to** also be conducted if a subject decides to prematurely withdraw/discontinue
Skin Biopsies					X[b]					X[b]			[b]Day 1 biopsies will be taken pre-dose. Day 28 biopsies will be taken 4 hours post-dose
UV threshold testing		X											
Photoprovocation			X[c, d]										Performed 24 hours after UV threshold testing. [c]PV occurs once every 24 hours for 3 days on Day-14, Day-13 & Day-12. [d] **If PV induced lesions appear at all 3 sites after Day -14 or Day -13, PV treatment can be stopped early**
Lesion induction assessment			<- ----X---->										
Lesion resolution assessment											X	X	
Clinical score					X		X			X			Components of the RCLASI as defined in Section 7.3 Assessments to be performed pre-dose
Local Tolerability Assessment					X	X	X	X	X	X	X		Assessments to be performed pre-dose and up to one hour following dosing on days of dosing
Dosing					X	X	X	X	X	X			Once daily
Randomisation					X								Pre-dose

Procedure	**Screening (up to Day -28)**	**Day -15**	**Day -14**	**Day -13 to -1**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up[a]**	[a] All procedures listed ~~should~~ **to** also be conducted if a subject decides to prematurely withdraw/discontinue
PK blood sample					X	X	X		X	X	X	X	Sampling timepoints: Day 1 = pre-dose; and 5hrs (±1 hr) Between Day 2 and Day13: one pre-dose sample or postdose sample with time recorded since last dose Day 14: predose sample Between Day 21 and Day27: one pre-dose sample or postdose sample with time recorded since last dose Day 28: one postdose sample with time recorded since last dose Between Day 29 and Day 42: one sample with time recorded since last dose Follow-up visit: one sample with sampling day recorded
AE/SAE Review	X	<----------X---------->											
Concomitant Medication Review	X	<----------X---------->											

Section 7.1.3 Time and Events Table Group B

Rationale for Change: Alteration to the frequency of pregnancy testing required throughout

REVISED TEXT:

Procedure	**Screening (up to Day -28)**	**Day -5 to -3**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up (between Day 43 to Day 56)[a]**	[a] All procedures listed ~~should also~~ **to** be conducted if a subject decides to prematurely withdraw/discontinue
Informed Consent	X										
Inc/Exc criteria assessment	X										
Demography	X										
Pregnancy Test (women)	X	~~X~~	X	~~X~~	X		~~X~~	~~x~~		X	~~Pregnancy testing between Day 1 & Day 28 should be performed once every 7 days. On days of dosing, test should be performed pre-dose~~ **Pregnancy testing to be performed at Screening, on Day 1 (pre-dose), Day 14 (pre-dose) and once during follow-up, with day recorded**
TSH, free T4, freeT3	X		X		X					X	
Vital Signs	X	X			X			X			
Safety Lab Samples (clin chem ,haematol, Urinalysis)	X	X	X		X			x		X	On days of dosing samples should be taken predose
Full Physical Exam	X									X	
Brief Physical Exam			X								Assessment to be performed pre-dose
12-lead ECG	X		X		X					X	On days of dosing

Procedure	**Screening (up to Day -28)**	**Day -5 to -3**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up (between Day 43 to Day 56)[a]**	[a] All procedures listed ~~should also~~ **to** be conducted if a subject decides to prematurely withdraw/discontinue
											assessments should be performed predose
SLE clinical assessment	X		X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose .
ANA, anti-dsDNA antibodies, anti-Ro and anti-La antibodies, HIV, Hep B, Hep C, FSH, Drug screen	X										
Lesion selection		X									Refer to Section 4.1 and Section 6.1
Skin Biopsies		X[b]						X[b]			[b]2 to 4 days healing time will be allowed prior to randomisation and the first dose. Day 28 biopsies will be taken 4 hours post-dose
Clinical score			X		X			X			
Local tolerability Assessment			X	X	X	X	X	X	X		Assessments to be performed pre-dose and up to one hour following dosing on days of dosing
Dosing			X	X	X	X	X	X			Once daily
Randomisation			X								Pre-dose

Procedure	**Screening (up to Day -28)**	**Day -5 to -3**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up (between Day 43 to Day 56)[a]**	[a] All procedures listed ~~should also~~ **to** be conducted if a subject decides to prematurely withdraw/discontinue
PK blood sample			X	X	X		X	X	X	X	Sampling timepoints: Day 1 = pre-dose; and 5hrs (±1 hr) Between Day 2 and Day13: one pre-dose sample or postdose sample with time recorded since last dose Day 14: predose sample Between Day 21 and Day27: one pre-dose sample or postdose sample with time recorded since last dose Day 28:one postdose sample with time recorded since last dose Between Day 29 and Day 42: one sample with time recorded since last dose Follow-up visit: one sample with sampling day recorded
AE/SAE Review	X										
Concomitant Medication Review	X										
Lesion									X	X	

Procedure	**Screening (up to Day -28)**	**Day -5 to -3**	**Day 1**	**Day 2 to Day 13**	**Day 14**	**Day 15 to Day 20**	**Day 21 to Day 27**	**Day 28**	**Day 29 to 42**	**Follow-up (between Day 43 to Day 56)[a]**	[a] All procedures listed ~~should also~~ **to** be conducted if a subject decides to prematurely withdraw/discontinue
resolution assessment											

Section 7.4.7 Clinical Safety Laboratory Assessments

Rationale for Change: Removal of non-required footnote number

REVISED TEXT:

- Serum or urine hCG Pregnancy test (as needed for women of child bearing potential) ~~2~~

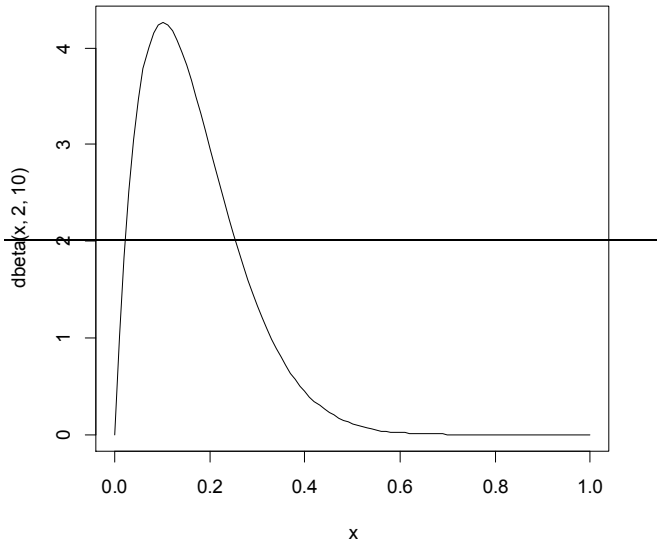
Section 9.2 Sample Size Considerations

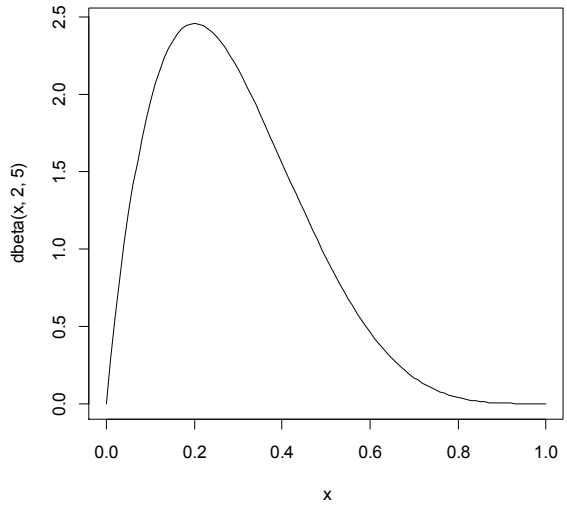
Rationale for Change: Amendment to the total number of subjects to be recruited to the study and sample size assumptions.

REVISED TEXT:

We will recruit approximately ~~50~~**25** patients with CLE into the study with the aim to randomise **approximately 20** ~~40~~ patients. Approximately ~~20~~ **10** patients will undergo PV in group A. PV response rates are estimated at 50% and we expect ~~10~~ **up to 5** PV positive patients to be randomised into the study. We aim to randomise ~~up to 30~~ **approximately 15** patients into group B of the study. All patients will be treated with both GSK2646264 and placebo on separate lesions (see Section 6.1 for details).

…..For group A, Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe 1 safety event in ~~10~~ **5** then the posterior distribution would be Beta (2, **5** ~~10~~), as outlined below:…..



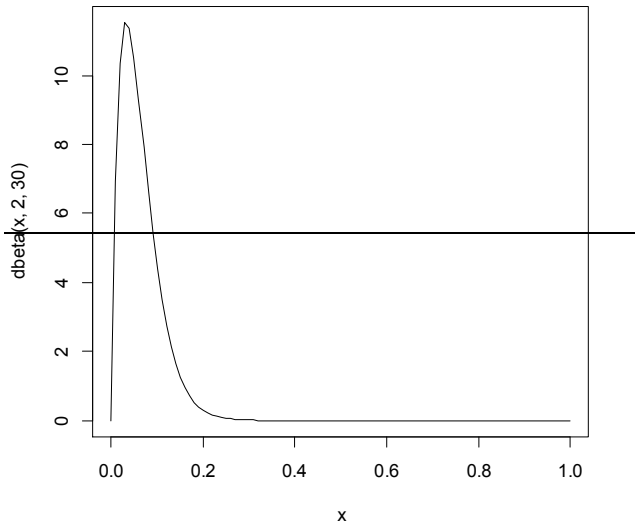


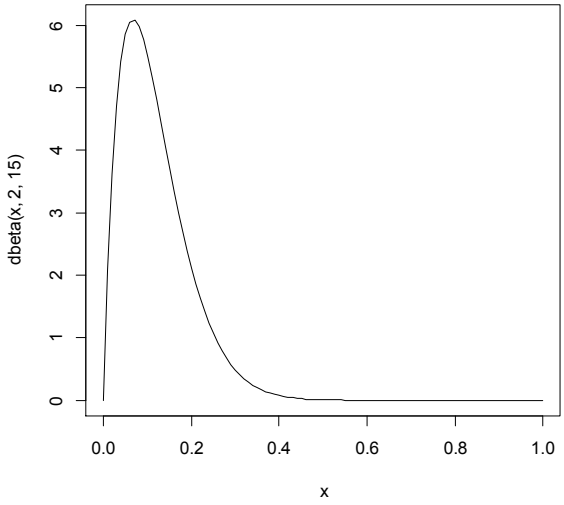
Where we can be 95% certain that the true probability of the safety event lies between **0.04** ~~0.02~~ and **0.64** ~~0.41.~~

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates **with 5 subjects in part A. Additionally**, i~~I~~f the number of subjects is lower than **5** ~~10~~ in group A, then the true incidence rates of safety events that could not be ruled out would change.

N completing the study	Number of particular safety events observed with active	Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out
5~~10~~	0	**46**~~29%~~
5~~10~~	2	**78**~~52%~~
4~~8~~	0	**52**~~34%~~
4~~8~~	1	**72**~~48%~~
4~~8~~	2	**85**~~60%~~

For group B, using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe 1 safety event in **15** ~~30~~ then the posterior distribution would be Beta (2, **15** ~~30~~), as outlined below:





Where we can be 95% certain that the true probability of the safety event lies between **0.02** ~~0.01~~ and **0.30** ~~0.17.~~

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates **with 15 subjects in part B. Additionally**, i If the number of subjects is lower than **15** ~~30~~ in group B, then the true incidence rates of safety events that could not be ruled out would change.

N completing the study	**Number of particular safety events observed with active**	**Upper limit of exact 95% CI indicating that a true incidence rate of x% could not be ruled out**
15~~30~~	0	**21**~~11~~%
15~~30~~	2	**38**~~21~~%
12~~28~~	0	**25**~~12~~%
12~~28~~	1	**36**~~18~~%
12~~28~~	2	**45**~~23~~%

~~A key secondary endpoint is to determine the effect of GSK2646264 on expression of IFN mRNA signature in skin biopsies in treated PV and existing CLE lesions. The estimate of standard deviation comes from existing data on subjects with CDLE [Braegelmann, 2016].~~

~~Variable~~	~~Gene~~	~~Sd~~	~~Estimated~~	~~10 subjects~~	~~30 subjects~~

	Name	log 2 scale	within SD	Estimated width of 95% CI of treatment difference on the log 2 scale	95% CI of the treatment ratio (if ratio is 1)	Estimated width of 95% CI of treatment difference on the log 2 scale	95% CI of the treatment ratio (if ratio is 1).
A_23_P6263	MX2	0.43	0.28	±0.465	(0.72, 1.38)	±0.243	(0.84, 1.18)
A_33_P3278200	MX2	0.60	0.39	±0.647	(0.64, 1.57)	±0.338	(0.79, 1.26)
A_23_P204087	OAS2	0.42	0.27	±0.448	(0.73, 1.36)	±0.234	(0.85, 1.18)
A_23_P17663	MX1	0.40	0.26	±0.432	(0.74, 1.35)	±0.225	(0.86, 1.17)
A_23_P23074	IFI44	0.43	0.28	±0.465	(0.72, 1.38)	±0.243	(0.84, 1.18)
A_24_P303091	CXCL10	0.98	0.64	±1.063	(0.48, 2.09)	±0.555	(0.68, 1.47)
A_33_P3343175	CXCL10	0.84	0.55	±0.913	(0.53, 1.88)	±0.477	(0.72, 1.39)

The following precision estimates are based on variability estimates from existing data on subjects with SCLE.

				10 subjects		30 subjects	
Variable	Gene Name	Sd log 2 scale	Estimated within SD	Estimated width of 95% CI of treatment difference on the log 2 scale	95% CI of the treatment ratio (if ratio is 1)	Estimated width of 95% CI of treatment difference on the log 2 scale	95% CI of the treatment ratio (if ratio is 1).
A_23_P6263	MX2	0.89	0.58	±0.963	(0.51, 1.95)	±0.503	(0.71, 1.42)
A_33_P3278200	MX2	0.87	0.57	±0.946	(0.52, 1.93)	±0.494	(0.71, 1.41)
A_23_P204087	OAS2	0.57	0.37	±0.614	(0.65, 1.53)	±0.321	(0.80, 1.25)
A_23_P17663	MX1	0.66	0.43	±0.714	(0.61, 1.64)	±0.373	(0.77, 1.30)
A_23_P23074	IFI44	0.12	0.08	±0.133	(0.91, 1.10)	±0.069	(0.95, 1.05)
A_24_P303091	CXCL10	1.43	0.94	±1.561	(0.34, 2.95)	±0.815	(0.57, 1.76)
A_33_P3343175	CXCL10	1.50	0.98	±1.627	(0.32, 3.09)	±0.85	(0.55, 1.80)

~~An exploratory endpoint of this study is to determine the effect of GSK2646264 on the extent of histological disease activity in PV and existing CLE lesions. Data presented in [Zahn, 2014] for parakeratosis, ballooning, necrosis, junctional inflammation and dermal infiltrate show a between subject standard deviation of between 0.44 and 0.67. Based on 10 subjects in group A it is estimated that the 95% confidence interval will be within 0.98 of the estimate of the treatment difference where the within subject SD is assumed to be 0.59. Based on 30 subjects in group B it is estimated that the 95% confidence interval will be within 0.51 of the estimate of the treatment difference where the within subject SD is assumed to be 0.59.~~

~~Between Subject standard deviation~~	~~Within subject SD approximation~~	~~10 Subjects. Estimated width of 95% CI~~	~~30 subjects. Estimated width of 95% CI~~
~~0.447~~	~~0.29~~	~~±0.481~~	~~±0.251~~
~~0.670~~	~~0.44~~	~~±0.731~~	~~±0.382~~
~~0.894~~	~~0.59~~	~~±0.980~~	~~±0.512~~

Section 9.3.2 Interim Analysis

Rationale for Change: Introduction of in-stream review of data

REVISED TEXT:

In this sponsor-unblinded bilateral design study, 1 or more unblinded data reviews, using all available data to date, may be carried out by senior managers (not involved in the study conduct) and/or study team members (involved in the study conduct) to aid in portfolio and budget decisions. These administrative reviews will have no impact on the ongoing study. Full details will be provided in the reporting and analysis plan prior to the first administrative review.

Section 9.4 Key Elements of Analysis Plan

Rationale for Change

REVISED TEXT:

~~Final analysis of groups A and B will be reported after all subjects in groups A and B respectively have completed their follow-up visit; this may be at the same time or different times depending on the relative rates of recruitment. Final analysis for group B will be reported after all subjects in group B have completed their follow-up visit.~~ **Final analysis of groups A and B will be reported together after all subjects in groups A (up to 5 subjects) and B (approximately 15 subjects) have completed their follow-up visit.**

Section References

Rationale for Change: Additional reference added

REVISED TEXT:

Posobiec LM, Cox EM, Solomon HM, Lewis EM, Wang K-f and Stanislaus D: A Probability Analysis of Historical Pregnancy and Fetal Data from Dutch Belted and New Zealand White Rabbit Strains from Embryo-Fetal Development Studies. Birth Defect Research (Part B) 2016; 107:76-84.

12.6.2. Protocol changes for Amendment 2 (04-Aug-2016) from the Protocol amendment 1 (13-June-2016)

Where the Amendment Applies
Amendment 2 applies to all site

Summary of Amendment Changes with Rationale

Changes have been made following review from BfArM and ethics, primarily to inclusion/exclusion criteria, and clarification of dose.

List of Specific Changes

Title Page, Authors

Rationale for change: Author's name was added.

REVISED TEXT

PPD **(II TAU),** PPD (PCPS), PPD (DMPK), PPD (QSci), PPD (CPSSO), PPD (II TAU), PPD (II TAU), PPD PPD (GCSP), PPD (CUC), PPD (CPMS)

Section 4.5 Dose Justification

1st Paragraph

Rationale for change: Dose to be applied was clarified to include details on total cream to be applied and to weigh cream to ensure amount of dose applied.

REVISED TEXT

GSK2646264 will be administered topically as a cream at 1% (w/w) strength.The maximum topically applied dose **to any subject at any time point** will be 10mg/cm^2 of cream over 90 cm^2 (**maximum of ~0.5% Body Surface Area as determined by Du Bois, 1916**). This equates to **a maximum of 900mg of cream and therefore** 9 mg of GSK2646264. A corresponding placebo will also be applied. **Cream will be weighed both before and after application.**

Section 5 Selection of Study Population and Withdrawal Criteria

2nd Paragraph

Rationale for change: Section was updated to specify groups to which inclusion/exclusion/withdrawal criteria apply.

REVISED TEXT

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator Brochure [GlaxoSmithKline Document Number: 2013N182566_02, GlaxoSmithKline Document Number 2015N268236_01 (Supplement 1) and GlaxoSmithKline Document Number 2016N281634_00 (Supplement 2)]

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential. **All inclusion/exclusion criteria and withdrawal criteria apply to subjects in both Part A and Part B, unless specifically stated otherwise.**

Section 5.2 Exclusion criteria

Rationale for change: Conditions for medical history and diagnostic test, were updated to add more details for subjects to be excluded, disease condition, withdrawal from study and inclusion of HIV test.

REVISED TEXT

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTC INTERVAL)
1. ALT >2xULN; 2. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) 3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 4. QTcF > 450 msec, or QTcF > 480 msec in subjects with Bundle Branch Block NOTES: • The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. • The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. • For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

5. History of any past or present benign or malignant skin conditions and disease, unless in the opinion of the investigator it will not compromise the subjects safety and quality of data.
6. **Subjects with active Systemic Lupus Erythematosus (SLE) and/or significant disease in any other organ than the skin, as judged by the Investigator after discussion with the medical monitor**
7. Subjects with a history of Graves disease
8. Subjects with a history of thyroid cancer.
9. Unable to refrain from vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half lives (whichever is longer) prior to the screening visit until the completion of the follow-up assessments, unless in the opinion of the Investigator, in consultation with the GSK Medical Monitor if required, the medication will not interfere with the study procedures or compromise subject safety.
10. Clinically significant abnormality in the hematological, clinical chemistry, or urinalysis screen, **that in the opinion of** the investigator after discussion with the medical monitor, **requires further investigation, medical intervention or poses a risk to the subject to participate in the trial.**
11. Subjects who start prohibited medications or therapies at any time during the study **will** ~~may~~ be withdrawn from the study. ~~Subjects who start prohibited medications or therapies may remain in the study only with the approval of the Medical Monitor and at the discretion of the Sponsor.~~

The following medications and therapies are prohibited at any time during the study:

- Use of other investigational agents (biologic or non-biologic; investigational applies to any drug not approved for sale in the country in which it is used).
- Co-enrolment into another study of an investigational agent or non-drug therapy.
- Use of biological agents (e.g., alemtuzumab, rituximab, ATG) during the clinical study or within 12 months to first dose of study treatment.

Use of other immunosuppressive drugs commonly used in SLE including Azathioprine, Methotrexate, Mycophenolate, Cyclophosphamide within 3 months to first dose of study treatment.

REVISED TEXT

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
15. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. **16. A positive HIV test at screening** 17. A positive pre-study drug screen. 18. Where participation in the study would result in donation of blood or blood products in excess of 450 ml within 3 months. 19. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 20. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day. Country Specific Exclusion criteria wording for Germany: 21. Subjects that are employees of either GlaxoSmithKline (sponsor) or one of the study centres (investigators). 22. Subjects who live in detention on court order or on regulatory action, see §40 subsection 1 sentence 3 no. 4 AMG. (Arzneimittelgesetz).

Section 5.4 Withdrawal/Stopping Criteria

Rationale for change: Withdrawal criteria specific for group A added and typo error was corrected.

REVISED TEXT

WITHDRAWAL (Specific for Group A ONLY)
1. A subject will be withdrawn from the study, if they demonstrate an excessive or adverse reaction to the photoprovocation, as judged by the Investigator after discussion with the medical monitor.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. In case a subject withdraws from study they should be encouraged to continue contraception for 28 days.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. ~~A subject~~ **If a subject** withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Section 5.4.3 Safety Related Study Specific Dose Adjustment Criteria

Rationale for change: Criteria for reporting AE of severe intensity was updated.

1st paragraph

REVISED TEXT

If AEs are of severe intensity and are similar across subjects, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK2646264, or if dose limiting toxicity (see Section 5.4.1), are observed in ~~2 or more subjects~~ **at least 2 subjects**, relevant reporting and discussion with the GSK medical monitor and the SRT will take place.

Section 7. Study Assessments and Procedures

Rationale for change: Laboratory test to be done at screening updated to make it consistent with the change done in Exclusion criteria.

REVISED TEXT

There is addition of **HIV, Hep B, Hep C, FSH, Drug screen** tests in Section 7.1.1, Group A

Procedure	Screening (up to Day -28)	Day -15	Day -14	Day -13 to -1	Day 1	Day 2 to Day 13	Day 14	Day 15 to Day 20	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
12-lead ECG	X				X		X					X	On days of dosing assessments should be performed predose
SLE clinical assessment	X				X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose .
ANA, anti-dsDNA , anti-Ro and anti-La antibodies**, HIV, Hep B, Hep C, FSH, Drug screen**	X												

There is addition of **HIV, Hep B, Hep C, FSH, Drug screen** tests in Section 7.1.3, Group B

Procedure	Screening (up to Day -28)	Day -5 to -3	Day 1	Day 2 to Day 13	Day 14	Day 15 to Day 20	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up (between Day 43 to Day 56)[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
12-lead ECG	X		X		X					X	On days of dosing assessments should be performed predose
SLE clinical assessment	X		X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose .
ANA, anti-dsDNA antibodies, anti-Ro and anti-La antibodies, **HIV, Hep B, Hep C, FSH, Drug screen**	X										

Section 7.4.6 Photo-provocation model

Rationale for change: Section was updated to include details on maximum UVA & UVB irradiation to be received

REVISED TEXT

Subjects will undergo UV threshold testing on six 4.5 cm^2 areas of the lower back each for UVA and UVB irradiation during screening. **The maximum UVA irradiation received will be 100 Jcm^{-2} and the maximum UVB will be 200 $mJcm^{-2}$ as per the method described by** Kuhn **(2011).**

Section 7.4.7 Clinial Safety Laboratory Assessments

Rationale for change: Laboratory test to be done was updated to make it consistent with the update done in Exclusion criteria and Time & Events Table.

Table 1

REVISED TEXT

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential</u>:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatise</td><td>Albumin</td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravity
• pH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td>• HIV
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)
• FSH and estradiol (as needed in women of non-child bearing potential only)
• Drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
• Serum or urine hCG Pregnancy test (as needed for women of child bearing potential) [2]
• Free T3</td></tr>
</table>

Laboratory Assessments	Parameters
	• Free T4 • TSH • ANA, Anti-ds DNA, Anti-Ro and Anti-La antibodies
NOTES : 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.4 and Appendix 2.	

Section 11 References

Rationale for Change: Reference updated due to addition of references in Section 4.5.

REVISED TEXT

Du Bois D, Du Bois EF, A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med, 1916; 17: 863-71

Section 12.1. Appendix 1-Abbreviation and Trademarks

Rational for change: There is an updation in abbreviation list

REVISED TEXT

AE	Adverse Event
BMI	**Body Mass Index**
BCR	**B-cell receptor**
CCLE	Chronic Cutaneous Lupus Erythematosus
CLE	Cutaneous Lupus Erythematosus
CONSORT	**Consolidated Standards of Reporting Trials**
CRF	**Case Report Form**
CV	**Cardio Vascular**
FcεR1	**Fc epsilon receptors**
FRP	Females of Reproductive Potential
FSH	**Follicle Stimulating Hormone**
FTIH	**First Time in Human**
GCP	**Good Clinical Practice**
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HIV	**Human Immuno-Deficiency Virus**
HRT	**Hormone Replacement Therapy**
IDSL	**Integrated Data Standards Library**
IEC	**Independent Ethics Committee**

IFN	Interferon
IRB	**Institutional Review Board**
LET	Lupus Erythematosus Tumidus
MALDI-MS	**Matrix Assisted Laser Desorption Ionization-Imaging Mass Specrometry**
mRNA	Messenger-Ribonucleaic Acid
MSDS	**Material Safety Data Sheet**
NOAEL	**No Observed Adverse Effect Level**
PD	**Pre-dose**
PK	**Pharmacokinetics**
pSYK	Phosporylated- Spleen Tyrosine Kinase
PV	Photoprovocation
QTcB	**QT interval corrected for heart rate according to Bazett's formula**
QTcF	**QT interval corrected for heart rate according to Fridericia's formula**
QoL	**Quality of Life**
RAP	**Reporting and Analysis Plan**
SAE	Serious Adverse Event
SCLE	Sub-acute Cutaneous Lupus Erythematosus
SD	**Standard Deviation**
SLE	**Systemic Lupus Erythematosus**
SRM	**Study Reference Manual**
SRT	**Safety Review Team**
SYK	**Spleen Tyrosine Kinase**

12.6.3. Protocol changes for Amendment 1 (13-June-2016) from the Original Protocol (18-May-2016)

Summary of Amendment Changes with Rationale

Changes have been made to the Time and events table to add another column day 15 to day 20 to highlight any study procedures being taken.

List of Specific Changes

Section 7.1.1 Group A

Rationale for change: Changes have been made to the Time and events table to add another column **day 15 to day 20** .

REVISED TEXT

Procedure	Screening (up to Day -28)	Day -15	Day -14	Day -13 to -1	Day 1	Day 2 to Day 13	Day 14	**Day 15 to Day 20**	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
Informed Consent	X												
Inc/Exc criteria assessment	X												
Demography	X												
Pregnancy Test (women)	X	X		X	X	X	X		X	x		X	Pregnancy testing between Day 1 & Day 28 should be performed once every 7 days. Pregnancy test on Day 1 will be pre-dose.
TSH, free T4, ,free T3	X				X		X					X	
Vital Signs	X	X			X		X			X			
Safety Lab Samples (clin chem, haematol, Urinalysis)	X	X		X	X		X			X		X	On days of dosing samples should be taken predose. Sample timepoints during the Day-13 to Day-1 period are as follows: – once weekly during visits to assess PV lesion development
Full Physical Exam	X											X	
Brief Physical Exam				X									Assessment to be performed pre-dose Sample timepoints during the Day-13 to Day-1 period are as follows: – once weekly

Procedure	Screening (up to Day -28)	Day -15	Day -14	Day -13 to -1	Day 1	Day 2 to Day 13	Day 14	**Day 15 to Day 20**	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
													during visits to assess PV lesion development
12-lead ECG	X				X		X					X	On days of dosing assessments should be performed predose
SLE clinical assessment	X				X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose .
ANA, anti-dsDNA , anti-Ro and anti-La antibodies	X												
Skin Biopsies					X[b]					X[b]			[b]Day 1 biopsies will be taken pre-dose. Day 28 biopsies will be taken 4 hours post-dose
UV threshold testing		X											
Photoprovocation			X[c]										Performed 24 hours after UV threshold testing. [c]PV occurs once every 24 hours for 3 days on Day-14, Day-13 & Day-12.
Lesion induction assessment			<- ----X----->										
Lesion resolution assessment											X	X	
Clinical score					X		X			X			Components of the RCLASI as defined in Section

Procedure	Screening (up to Day -28)	Day -15	Day -14	Day -13 to -1	Day 1	Day 2 to Day 13	Day 14	**Day 15 to Day 20**	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
													7.3 Assessments to be performed pre-dose
Local Tolerability Assessment					X	X	X	X	X	X	X		Assessments to be performed pre-dose and up to one hour following dosing on days of dosing
Dosing					X	X	X	X	X	X			Once daily
Randomisation					X								Pre-dose
PK blood sample					X	X	X		X	X	X	X	Sampling timepoints: Day 1 = pre-dose; and 5hrs (±1 hr) Between Day 2 and Day13: one pre-dose sample or postdose sample with time recorded since last dose Day 14: predose sample Between Day 21 and Day27: one pre-dose sample or postdose sample with time recorded since last dose Day 28: one postdose sample with time recorded since last dose Between Day 29 and Day 42: one sample with time recorded since last dose Follow-up visit: one sample with

Procedure	Screening (up to Day -28)	Day -15	Day -14	Day -13 to -1	Day 1	Day 2 to Day 13	Day 14	**Day 15 to Day 20**	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
													sampling day recorded
AE/SAE Review	X		<----------X---------->										
Concomitant Medication Review	X		<----------X---------->										

Section 7.1.3 Group B

Rationale for change: Changes have been made to the Time and events table to add another column **day 15 to day 20**.

REVISED TEXT

Procedure	Screening (up to Day -28)	Day -5 to -3	Day 1	Day 2 to Day 13	Day 14	**Day 15 to Day 20**	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up (between Day 43 to Day 56)[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
Informed Consent	X										
Inc/Exc criteria assessment	X										
Demography	X										
Pregnancy Test (women)	X	X	X	X	X		X	x		X	Pregnancy testing between Day 1 & Day 28 should be performed once every 7 days. On days of dosing, test should be performed pre-dose
TSH, free T4, freeT3	X		X		X					X	
Vital Signs	X	X			X			X			
Safety Lab Samples (clin chem ,haematol, Urinalysis)	X	X	X		X			x		X	On days of dosing samples should be taken predose
Full Physical Exam	X									X	
Brief Physical Exam			X								Assessment to be performed pre-dose
12-lead ECG	X		X		X					X	On days of dosing assessments should be performed predose
SLE clinical assessment	X		X					X		X	On days of dosing assessment as defined by the investigator to be performed pre-dose .
ANA, anti-dsDNA antibodies, anti-Ro and anti-La antibodies	X										
Lesion selection		X									Refer to Section 4.1 and Section 6.1
Skin Biopsies		X[b]						X[b]			[b]2 to 4 days healing time will be allowed prior to

Procedure	Screening (up to Day -28)	Day -5 to -3	Day 1	Day 2 to Day 13	Day 14	**Day 15 to Day 20**	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up (between Day 43 to Day 56)[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
											randomisation and the first dose. Day 28 biopsies will be taken 4 hours post-dose
Clinical score			X		X			X			
Local tolerability Assessment			X	X	X	X	X	X	X		Assessments to be performed pre-dose and up to one hour following dosing on days of dosing
Dosing			X	X	X	X	X	X			Once daily
Randomisation			X								Pre-dose

Procedure	Screening (up to Day -28)	Day -5 to -3	Day 1	Day 2 to Day 13	Day 14	**Day 15 to Day 20**	Day 21 to Day 27	Day 28	Day 29 to 42	Follow-up (between Day 43 to Day 56)[a]	[a] All procedures listed should also be conducted if a subject decides to prematurely withdraw/discontinue
PK blood sample			X	X	X		X	X	X	X	Sampling timepoints: Day 1 = pre-dose; and 5hrs (±1 hr) Between Day 2 and Day13: one pre-dose sample or postdose sample with time recorded since last dose Day 14: predose sample Between Day 21 and Day27: one pre-dose sample or postdose sample with time recorded since last dose Day 28:one postdose sample with time recorded since last dose Between Day 29 and Day 42: one sample with time recorded since last dose Follow-up visit: one sample with sampling day recorded
AE/SAE Review	X										
Concomitant Medication Review	X										
Lesion resolution assessment									X	X	