Statistical Analysis Plan

A two-part trial to evaluate the safety, tolerability, clinical effect and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis

Confidential

bioskin GmbH • Burchardstrasse 17 • 20095 Hamburg • Germany

SIGNATURE PAGE

PPD

Manager, Clinical Pharmacology, GlaxoSmithKline

PPD

Senior Director, Clinical Statistics, GlaxoSmithKline

PPD

Manager, Clinical Programming, GlaxoSmithKline

PPD PhD

Principal Statistician, Clinical Statistics, GlaxoSmithKline

PPD PhD

Senior Clinical Trial Manager, bioskin GmbH

PPD

Head Biostatistics, bioskin GmbH

.

Table of contents

(continued)

Table of contents (continued)

Abbreviations and definitions

%CVb	between subject coefficient of variation
ACTH	adrenocorticotropic hormone
AE	adverse events
ALT	alanine transaminase
API	active pharmaceutical ingredient
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CI	confidence interval
CPMS	Clinical Pharmacology Modelling and Simulation
CRF	case report form
CTP	clinical trial protocol
CV	cardiovascular
D	day
ECG	electrocardiogram
eCRF	electronic case report form
FNRP	female of non-reproductive potential
g	gram
GI	giga
GSK	GlaxoSmithKline
H	hour
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
Hep	hepatitis
HIV	human immunodeficiency virus
HPLC-MS	High-performance liquid chromatography-mass spectrometry
IMP	investigational medicinal product
L	liter
LLN	lower limit of normal
LOCF	last observation carried forward
msec	millisecond
MALDI	matrix assisted laser desorption ionization
Max	maximum
MedDRA	medical dictionary for regulatory activities
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
Min	minimum
mmHg	millimeter of mercury
mol	mole

mRNA	messenger ribonucleic acid
n	non-missing observations
NOAEL	no observed adverse effect level
OC	observed cases
PASI	psoriasis area and severity index
PCI	potential clinical importance
PD	pharmacodynamic
PDF	portable document format
PGA	physician's global assessment
PK	pharmacokinetic
PP	per protocol
RBC	red blood cells
RNA	ribonucleic acid
RTF	rich text format
SAE	serious adverse events
SAP	statistical analysis plan
SAS	Statistical Analysis System
sec	seconds
ss	steady state
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate-pyruvate transaminase
TEAE	treatment emergent adverse event
TPSS	target plaque severity score
ULN	upper limit of normal
U	unit
UV	ultraviolet
WBC	white blood cells

1 Overview

This Statistical Analysis Plan (SAP) is issued to provide a comprehensive and detailed description of strategy, rationale, and statistical technique that will be used to evaluate the safety, tolerability and systemic exposure of topically applied GSK2981278 in subjects with plaque psoriasis.

The credibility of the study findings will be ensured by pre-specifying the statistical approaches to the analysis of the study data prior to unblinding of the randomization schedule. This SAP is based on the clinical trial protocol number 203820 (GSK document number 2016N275350_01), dated December 13, 2016.

1.1 Background / rationale

In the first clinical trial of GSK2981278, once daily treatment of GSK2981278 ointment (at 0.03%, 0.1%, 0.8%, and 4%) on small test fields (1.13 cm2) of stable plaque(s) over 19 days appeared to be well tolerated but did not show reduction in psoriatic infiltrate thickness. It is unclear whether the apparent lack of effect on infiltrate thickness in the first-time-in-human study was due to the very small surface area treated, the relatively short duration of exposure, or both, therefore, the present study will evaluate the safety, tolerability, clinical effect, and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis by treating all plaques on the body wholly for 8 weeks. The results of this study will provide preliminary information on the safety, tolerability, and effect of the GSK2981278 ointment on plaque psoriasis at the highest safe and feasible concentration to guide subsequent development strategy.

1.2 Objectives

Part A	
Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of topically applied GSK2981278 in subjects with plaque psoriasis	• Incidence and nature of adverse events (AEs) and serious adverse events (SAEs) • Application site tolerability assessment score • Change in clinical laboratory parameters, vital signs, and electrocardiogram (ECG) from baseline
• To evaluate the systemic exposure of GSK2981278 following topical application in subjects with plaque psoriasis	• Plasma concentrations of GSK2981278
Secondary	
• To evaluate the clinical effect following topical application of GSK2981278 in subjects with plaque psoriasis	• Mean percent change in Target Plaque Severity Score (TPSS) from baseline to Week 8 • Mean percent change in Physician's Global Assessment (PGA) score from baseline to Week 8 • Mean percent change in Psoriasis Area and Severity Index (PASI) from baseline to Week 8
Exploratory	
• To evaluate the effect of GSK2981278 ointment on relevant gene expression	• Fold change in messenger ribonucleic acid (mRNA) biomarkers from baseline to Week 8 in skin biopsy samples
• To investigate the delivery profile of GSK2981278 into the psoriatic skin following repeat topical applications	• Quantification of GSK2981278 in the skin biopsy using Matrix Assisted Laser Desorption Ionization (MALDI) imaging mass spectrometry or High-performance liquid chromatography-mass spectrometry (HPLC-MS) at Week 8
• To evaluate the effect of GSK2981278 ointment on subject-reported outcomes	• Mean percent change in Psoriasis Symptom Diary score from baseline to each study visit
• To evaluate the potential metabolites of GSK2981278 in plasma, urine, and skin from biopsies in pooled subject samples, as data allow	• Identification of any compound-derived metabolite(s) from plasma and urine and if possible estimation of relative amounts of drug related material • Quantification of GSK2981278-derived metabolite(s) in the skin biopsy using MALDI imaging mass spectrometry or HPLC-MS at Week 8

Part B	
Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of topically applied GSK2981278 and its vehicle in subjects with plaque psoriasis	• Incidence and nature of AEs and SAEs • Application site tolerability assessment score • Change in clinical laboratory parameters, vital signs, and ECG from baseline
• To evaluate the clinical effect of topically applied GSK2981278 relative to vehicle control in subjects with plaque psoriasis	• Mean percent change in TPSS from baseline to Week 8 • Mean percent change in PGA score from baseline to Week 8 • Mean percent change in PASI from baseline to Week 8
Exploratory	
• To explore exposure-response relationship of sparse systemic exposures with the clinical endpoints (by performing population Pharmacokinetic (PK)/Pharmacodynamic (PD) analysis, if required), as data allows	• Plasma concentrations of GSK2981278 and clinical endpoints assessed to determine the clinical effect (e.g. TPSS, PGA, and PASI)
• To evaluate the effect of GSK2981278 ointment on subject-reported outcomes	• Mean percent change in Psoriasis Symptom Diary score from baseline to each study visit

1.3 Modifications from the statistical section in the protocol

Not applicable.

2 Investigational plan

2.1 Study design and randomization

Overall design

This is a single-center, 2-part Phase I/IIa study to evaluate the safety, tolerability, clinical effect and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis. Drug delivery into the skin and changes in the relevant biomarkers will be explored using skin punch biopsies as well.

- **Part A**: open label, single arm study
- **Part B**: double-blind, randomized, 2-arm, parallel-group, vehicle-controlled study

After completion of Week 4 assessments and Week 8 assessments in Part A, the Sponsor will review the safety, tolerability, PK and clinical effect data. If data demonstrates a mean percent reduction of 40% or greater in TPSS and systemic exposure levels below the no observed adverse effect level (NOAEL) determined in the pre-clinical toxicity studies without significant safety or tolerability issues at either time point, the study will proceed to Part B.

After the Sponsor's review of Week 8 data in Part A against the pre-defined criteria, the Sponsor decided not to proceed to Part B of the trial, as the threshold level of reduction in TPSS was not

reached. In the following the trial design and planned analytical methods for Part A and Part B will be given, while detailed analyses will be provided for Part A only.

Treatment arms and duration

Each part of this study will consist of 3 periods: the screening period of up to 4 weeks, the treatment period of 8 weeks, and the follow-up period of 2 weeks. Study visits will occur at Screening; Baseline; Weeks 1, 4, and 8 during the treatment period; and Week 10 for follow-up, which will be 2 weeks after the last application of study treatment. Additional visits may occur, as needed, for early withdrawal or to follow-up on any skin reactions or ongoing AEs. A subject's total duration of study participation will be approximately 14 weeks.

In **Part A**, subjects will receive topical application of GSK2981278 4% ointment to all affected areas of the body twice daily for 8 weeks

In **Part B**, subjects will receive topical application of either GKS2981278 ointment or the vehicle ointment, according to the randomization, to all affected areas of the body twice daily for 8 weeks. The starting concentration of GSK2981278 in Part B will be determined based on Part A data review.

In both Parts, the subjects will receive 113 applications during the 8 weeks (Day 1 to Day 57) of treatment period.

The concentration of GSK2981278 may be lowered to 2% or 0.8% in Part A and/or Part B based on the newly available safety and tolerability data. See clinical trial protocol (CTP), section 6.4 for planned dose adjustments.

Treatment assignment

In **Part A**, all subjects will receive 4% ointment of GSK2981278.

In **Part B**, subjects will be assigned to ointment of GSK2981278 or the vehicle ointment in accordance with the randomization schedule generated by GlaxoSmithKline (GSK), prior to the start of the study, using validated internal software. The starting concentration of GSK2981278 in Part B will be determined based on Part A data review.

Once a randomization number has been assigned to a subject, it must not be re-assigned to a different subject.

The concentration of GSK2981278 may be lowered to 2% or 0.8% in Part A and/or Part B based on the newly available safety and tolerability data. See CTP, section 6.4 for planned dose adjustments.

Blinding

Part A will be an open-label study.

Part B will be a double-blind study (see CTP, section 6.5 for details).

Type and number of subjects

In **Part A**, eight adult subjects with chronic stable plaque psoriasis will be enrolled. If subjects prematurely discontinue the study treatment, additional replacement subjects may be recruited at the discretion of the Sponsor in consultation with the investigator.

In **Part B**, approximately 18 adult subjects with chronic stable plaque psoriasis will be randomized with an allocation ratio of 2:1 to GSK2981278 ointment or vehicle ointment to have at least 15 evaluable subjects who comply closely with the protocol (e.g. have sufficient exposure and critical assessments completed). The starting concentration of GSK2981278 in

Part B will be determined based on Part A data review. Subjects who were enrolled in Part A will not be eligible to participate in Part B.

If the concentration of GSK2981278 is lowered in either part of the study, additional subjects may be enrolled to have the minimum evaluable subjects in that part treated with the lower concentration of study treatment.

Compliance with study treatment administration

Subjects will be instructed to record the time of the study treatment application or reason for missed application for each planned study treatment administration. At each post baseline study visit, subjects will be asked to provide information from the study diary to study personnel regarding their compliance with study product use. Subjects should bring their tube(s) of study treatment with them to each visit for study personnel to weigh and document the amount used.

When subjects are dosed at the site, they will self-apply study treatment under the direction and supervision of the investigator or designee. The date and time of each dose administered in the clinic will be recorded in the source documents. The weight of the tube of ointment will be collected before and after the study treatment application at the site.

Analysis

No formal hypothesis tests are planned. Descriptive statistics will be used to assess the key objectives of this study.

2.2 Sample size justification

Sample size is based on feasibility and the estimated number of subjects expected to provide reasonable information on the key objectives of the study.

For **Part A**:

Summary statistics, such as mean % of reduction in TPSS, mean % reduction in PGA and mean % of reduction in PASI will be estimated. With 8 evaluable subjects, precisions on these estimates are assessed as below.

Endpoint	Assumptions	Sample Size	95%CI estimate
Mean % reduction in TPSS	50% reduction with 20% standard deviation will be observed	N=8	33.3% - 66.7%
Mean % reduction in PGA	50% reduction with 30% standard deviation will be observed	N=8	24.9%-75.1%
Mean % reduction in PASI	50% reduction with 25% standard deviation will be observed	N=8	29.1% -70.9%

For **Part B**:

With 15 subjects (10 in GSK2981278 arm and 5 in the Vehicle arm), the power to detect difference between GSK2981278 arm and the vehicle arm in terms of TPSS reduction, and PASI reduction are assessed below:

Endpoint	Assumptions	Sample Size (API:Vehicle)	Power to reject* H_0: API=Vehicle (Alpha=5%)
Mean % reduction in TPSS	50% reduction in GSK arm and 20% reduction in Vehicle with 20% standard deviation will be observed	N=10:5	71.7%
Mean % reduction in PASI	50% reduction in GSK arm and 10% in Vehicle with 20% standard deviation will be observed	N=10:5	92.1%

*2-sample t test
API- Active Pharmaceutical Ingredient

2.3 Study plan

2.3.1 Time and events table for Part A

Procedure	Screening	Treatment Period						Follow-up	Notes
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (±2 days)	**Day 15** (±2 days)	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Screening and Safety assessments									
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Demography	X								
Medical history/family history (includes substance usage, CV medical history and family history of premature CV disease)	X								Substances: Drugs, alcohol and tobacco
Prior and Concomitant Medication review (including prior therapy for psoriasis)	X	X		X	X		X	X	
Fitzpatrick Skin Type Classification	X								
Brief physical exam (including height and weight)	X						X		Brief physical exam including weight only on Day 57
12-lead Electrocardiogram	X	X			X		X		Triplicate ONLY if first reading is outside the eligibility criteria threshold value or the stopping criteria threshold value.
Vital sign	X	X		X	X		X		Vital signs include heart rate, blood pressure and oral temperature. Ideally, heart rate and blood pressure will be obtained after the subject has been resting in a seated or supine position for at least 5 minutes.

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (±2 days)	**Day 15** (±2 days)	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
HIV, Hep B and Hep C screen	X								If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Urine pregnancy test (FNRP)	X								
Laboratory assessments (include liver chemistries) and urinalysis	X	X		X	X		X		Urinalysis: On Days 1, 29, and 57, urine PK sample can be used.
AE/SAE review		X	X	X	X	X	X	X	Visits at Day 8 and Day 43 do not need to be office visits. This information may be collected via a phone call with the subject. On these days subject will be asked about application site tolerability also.
Application site tolerability		X		X	X		X		See CTP, section 7.5.7
Enrollment to study									
Identify and mark target lesion for TPSS		X							
Identify and mark area for biopsy collection		X							
Dispense tubes of study treatment		X		X	X				
Study treatment application		←----------					----------→		On clinic visit days, the morning application will be done in the clinic
Review compliance diary			X	X	X	X	X		Subjects will use a diary to record daily applications of study treatment and reasons for any missed applications On Day 8 and Day 43, subjects will be asked about compliance via phone.
Collect and weigh tubes of study treatment		X		X	X		X		
Efficacy assessments									
Psoriasis Symptom Diary	X	X		X	X		X		To be completed by subject before any other assessments at a clinic visit
Target Plaque Severity Score (TPSS)	X	X		X	X		X		
Physician Global Assessment (PGA)	X	X		X	X		X		

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (±2 days)	**Day 15** (±2 days)	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Psoriasis Area Severity Index (PASI)		X		X	X		X		
%BSA affected	X	X		X	X		X		
%BSA treated		X		X	X		X		
Pharmacokinetics									
Plasma sample for GSK2981278		X		X	X		X		Day 1, Day 29, and Day 57: pre-dose, and 1h, 2h, 4h, 6h, 8h, and 10h post morning dose Day 15: pre-dose and 2h post morning dose
Plasma sample for metabolite(s)		X					X		Pre-dose, and 1h, 2h, 4h, 6h, 8h, and 10h post morning dose.
Urine sample for metabolite(s)		X					X		Pre-dose urine on Day 1, 0-10h pool Two aliquots to be made for metabolite analysis and urinalysis. See CTP, section 7.6.2
Other assessments									
Skin punch biopsy		X					X		4 mm biopsy before study treatment application. 2 at Baseline (1 from non-lesional skin;1 from lesional skin-both for gene expression analyses) 2 at Day 57 (1 from lesions skin for gene expression analyses;1 from lesional skin for drug level)
Biopsy wound assessment				X				X	
Photograph of target lesion		X					X		

2.3.2 Time and events table for Part B

Procedure	Screening	Treatment Period						Follow-up	Notes
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (± 2 days)	**Day 15 (± 2 days)**	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Screening and Safety assessments									
Informed consent	X								
Inclusion and exclusion criteria	X	X							Will be assessed prior to randomization
Demography	X								
Medical history/family history (includes substance usage, CV medical history and family history of premature CV disease)	X								Substances: Drugs, alcohol and tobacco
Prior and Concomitant Medication review (including prior therapy for psoriasis)	X	X		X	X		X	X	
Fitzpatrick Skin Type Classification	X								
Brief physical exam (including height and weight)	X						X		Brief physical exam including weight on D57
12-lead Electrocardiogram	X	X			X		X		
Vital sign	X	X		X	X		X		Vital signs include heart rate, blood pressure and oral temperature. Ideally, heart rate and blood pressure will be obtained after the subject has been resting in a seated or supine position for at least 5 minutes.
HIV, Hep B and Hep C screen	X								If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Urine pregnancy test (FNRP)	X								

Procedure	Screening	Treatment Period						Follow-up	Notes
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (± 2 days)	**Day 15 (± 2 days)**	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Laboratory assessments (include liver chemistries) and urinalysis	X	X		X	X		X		
Genetic sample		X							Informed consent for optional,genetic research must be obtained before collecting a sample. Pre-dose & post-randomisation
AE/SAE review		X	X	X	X	X	X	X	Visits at Day 8 and Day 43 do not need to be office visits. This information may be collected via a phone call with the subject. On these days subject will also be asked about application site tolerability.
Application site tolerability		X		X	X		X		See CTP, section 7.5.7
Enrollment to study									
Identify and mark target lesion for TPSS		X							
Randomisation		X							
Dispense tubes of study treatment		X		X	X				
Study treatment application		←----------					----------→		On clinic visit days, the morning application will be done in the clinic
Review compliance diary			X	X	X	X	X		Subjects will use a diary to record daily applications of study treatment and reasons for any missed applications. On Day 8 and Day 43, subjects will be asked about compliance via phone or text message.
Collect and weigh tubes of study treatment		X		X	X		X		
Efficacy assessments									
Psoriasis Symptom Diary	X	X		X	X		X		To be completed by subject before any other assessments at a clinic visit
Target Plaque Severity Score (TPSS)	X	X		X	X		X		

Procedure	**Screening**	**Treatment Period**						**Follow-up**	**Notes**
Study Days (± specified no. of days)	**Day –28 to -1**	**Day 1 (Baseline)**	Day 8 (± 2 days)	**Day 15 (± 2 days)**	**Day 29 (±3 days)**	Day 43 (±3 days)	**Day 57 (±3 days)**	**2 weeks post-last dose (±3 days)**	Subjects who withdraw early from the study should complete the Day 57 visit assessments and subsequently enter follow-up period. Visits at Day 8 and Day 43 do not need to be clinic visits. Indicated information can be collected via a phone call with the subject.
Physician Global Assessment (PGA)	X	X		X	X		X		
Psoriasis Area Severity Index (PASI)		X		X	X		X		
%BSA affected	X	X		X	X		X		
%BSA treated		X		X	X		X		
Pharmacokinetics									
Plasma sample for GSK2981278		X		X	X		X		Day 1: between 3 and 12h post morning dose Day 15: pre-dose Days 29 and 57: within 12 h of morning dose
Other assessments									
Photograph of target lesion		X					X		

3 Statistical and analytical procedures

3.1 Definitions

The following definitions apply:

Screen failure

A subject who signs the informed consent but is not enrolled into the study. See 'Enrolled analysis set' in section 3.3.4 for the definition of enrollment.

Study day

The number of days from date of the Day 1 visit:

study day = missing,
If date of assessment or event is missing

study day = date of assessment or event - date of the Day 1 visit,
If date of assessment or event < date of the Day 1 visit,

study day = date of assessment or event - date of the Day 1 visit + 1,
If date of assessment or event ≥ date of the Day 1 visit

Study treatment

Any combination of products received by the subject as per the protocol design

On-treatment phase

The on-treatment phase will be defined as the period starting with the first application of study treatment and ending with the last application of study treatment.

Completed subject

A completed subject is one who has completed all phases of the study including the follow-up visit.

Past medical conditions

Medical conditions resolved (not on-going) prior to the start date of the study treatment , i.e. with medical condition start date missing or before study treatment start date and a not completely missing stop date before study treatment start date.

Current medical conditions

Medical conditions unresolved (on-going) at the study treatment start, i.e. if any of the following conditions hold:

- Medical condition start date is before study treatment start date and stop date is on or after study treatment start date or completely missing.
- Medical condition start date is completely missing and stop date is on or after study treatment start date.

- Both, start date and stop date for a medical condition are completely missing.

Prohibited medications and non-drug therapies

Prohibited concomitant medications, products, and procedures (Table 1) are not to have been used from the defined periods before the first study treatment applications at the Day 1 visit and throughout the study.

Table 1 Prohibited concomitant medications, products, and procedures

Prohibited medications, products, and procedures:	**Prohibited period before Day 1**
Biologic agents: (e.g., alefacept 24 weeks; etanercept 12 weeks; ustekinumab 15 weeks)	5 half-lives
Oral retinoids (e.g., acitretin or isotretinoin)	12 weeks
Cyclosporin, interferon, methotrexate, fumaric acid or other systemic immunosuppressive or immunomodulating agents (e.g., mycophenolate or tacrolimus)	4 weeks
Other investigational products or procedures	4 weeks or 5 half-lives, whichever is longer
Systemic corticosteroids or adrenocorticotropic hormone (ACTH) analogs	4 weeks
Systemic anticoagulants (e.g. warfarin, heparin, low molecular weight heparin, etc.)	5 half-lives
Immunizations (influenza vaccine will be allowed)	2 weeks
Topical treatments: corticosteroids, immunomodulators, anthralin (dithranol), Vitamin D derivatives, retinoids, coal tar (used on the body).	2 weeks
Drugs known to possibly worsen psoriasis (unless on a stable dose for >12 weeks), such as, but not limited to: β-blockers (eg, propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin	2 weeks
Any other topical therapy (including emollients) on psoriasis lesions treated in this study **Note**: Emollients may be used if Investigator, in consultation with the Medical Monitor, allows the use during a dosing holiday due to application site reaction. (See Topical Application Site Tolerability Stopping Criteria, below)	1 day
Phototherapy including psoralen plus UVA (PUVA)	2 weeks

Prior medication or therapies

Medication or therapy with start date missing or before study treatment start date and a not completely missing stop date before study treatment start date .

Concomitant medications or therapies

Medication or therapy occurring during the treatment period or follow-up, i.e. if any of the following conditions hold:

- Medication or therapy start date is before study treatment start date and stop date is on or after study treatment start date or completely missing.
- Medication or therapy start date is on or after study treatment start date and on or before last visit date.
- Medication or therapy start date is missing and stop date is on or after study treatment start date.
- Both, start date and stop date for a medication or therapy are completely missing.

Potential clinical importance (PCI) ranges

Table 2 Haematology analytes: Potential clinical importance (PCI) ranges

Lab test		Low	High
WBC (GI/L)		≤ 0.67 x LLN	≥ 1.82 x ULN
Neutrophil (GI/L)		≤ 0.83 x LLN	
Hemoglobin (G/L)	male		≥ 1.03 x ULN
	female		≥ 1.13 x ULN
Hematocrit (Fraction of 1)	male		≥ 1.02 x ULN
	female		≥ 1.17 x ULN
Platelet count (GI/L)		≤ 0.67 x LLN	≥ 1.57 x ULN
Lymphocytes (GI/L)		≤ 0.81 x LLN	

Table 3 Chemistry analytes: Potential clinical importance (PCI) ranges

Lab test	Low	High
Albumin (mmol/L)	≤ 0.86 x LLN	
Calcium (mmol/L)	≤ 0.91 x LLN	≥ 1.06 x ULN
Glucose (mmol/L)	≤ 0.71 x LLN	≥ 1.41 x ULN
Potassium (mmol/L)	≤ 0.86 x LLN	≥ 1.10 x ULN
Sodium (mmol/L)	≤ 0.96 x LLN	≥ 1.03 x ULN

Table 4 Liver function test analytes: Potential clinical importance (PCI) ranges

Lab test	High
ALT/SGPT (U/L)	≥ 2 x ULN
AST/SGOT (U/L)	≥ 2 x ULN
Alkaline phosphatase (U/L)	≥ 2 x ULN

Lab test	High
Total Bilirubin (µmol/L)	≥ 1.5 x ULN
Total Bilirubin (µmol/L) and ALT (U/L)	≥ 1.5 x ULN Total Bilirubin and ≥ 2 x ULN ALT

Table 5 ECG: Potential clinical importance (PCI) ranges

ECG Parameter*	Low	High
Absolute QTc interval (msec)		> 450
Increase from baseline QTc (msec)		> 60
PR interval (msec)	< 110	> 220
QRS interval (msec)	< 75	> 110

* for specifications of QTc see section on QTc stopping criteria below

Table 6 Vital signs: Potential clinical importance (PCI) ranges

VS Parameter	Low	High
Systolic Blood Pressure (mmHg)	< 85	> 160
Diastolic Blood Pressure (mmHg)	< 45	> 100
Heart Rate (bpm)	< 40	> 110

Phase II liver chemistry stopping criteria

Liver safety required actions and follow-up assessments can be found in CTP, Appendix 6.

QTc stopping criteria

The same QT correction formula must be used for each individual subject to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled. QTcB will be utilized for this study.

The QTcB should be based on single QTcB values electrocardiograms. If QTcB is outside of the threshold value of the stopping criteria shown below, triplicate ECGs will be performed over a brief (e.g., 5-10 minute) recording period with the QTcB values averaged.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTcB > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTcB > 60 msec

For patients with underlying bundle branch block, follow the discontinuation criteria listed below:

Table 7 QTc stopping criteria for patients with underlying bundle branch block

Baseline QTcB with Bundle Branch Block	Discontinuation QTcB with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

Topical application site tolerability stopping criteria

If a subject experiences application site reaction of grade 3 (severe) or 4 (very severe) on the topical application site tolerability scale (Table 14), study treatment will be discontinued permanently.

If a subject experiences application site reaction of grade 2 (moderate) on the topical application site tolerability scale with cracking, study treatment WILL be temporarily discontinued and the subject will be put on a dosing holiday until the irritation resolves. If a subject experiences application site reaction of grade 2 (moderate) without cracking, investigator MAY temporarily discontinue study treatment and put the subject on a dosing holiday in consultation with the subject and medical monitor until the irritation resolves. No rescue medication will be allowed during a dosing holiday. Investigator in consultation with the Medical Monitor may allow the use of emollients during the dosing holiday. The dosing holiday will be limited to once in each subject over the course of the study and the duration will not exceed 1 week. After the dosing holiday, the subject may be retreated with the study treatment if the irritation resolves.

At the time of permanent (grade 3 or 4) or temporary (grade 2) treatment discontinuation due to the application site intolerability and at the time of treatment restart (if applicable, after a dosing holiday), photographic documentation of a representative area of irritation (preferably the target lesion or the vicinity, if affected) will be taken.

Treatment emergent adverse events (TEAEs)

AEs occurred or worsened within the window of the first application of study treatment and 15 hours after the last application of study treatment, if any of the following conditions hold:

- AE onset date is on or after study treatment start date and on or before 15 hours after the last application of study treatment.
- AE onset date is completely missing and AE stop date is on or after study treatment start date.
- date of the last application is missing and AE stop date or AE onset date is after study treatment start date.
- both AE onset date and stop date are completely missing.

The 15 hours comes from the roughly predicted value of 5 times half-life of GSK2981278 in animal studies.

Baseline

Last observation collected prior to the first application of study treatment.

Last observation carried forward (LOCF)

The last observed value (either scheduled or unscheduled) carried forward and used for all subsequent scheduled points where the data is missing. Only efficacy data up to Day 57 visit will be imputed. No imputation for the Follow-up visit will be carried out.

Change from baseline

Change from baseline will be calculated by the post-baseline assessment value minus the baseline assessment value.

% Change from baseline

% Change from baseline will be calculated by the formula: (change from baseline / the baseline assessment value) * 100.

3.2 Analysis variables

3.2.1 Pharmacokinetic variables

The planned Pharmacokinetic variables are described below. Analysis of compound-related metabolites in plasma, GSK2981278 and related metabolites in urine and GSK2981278 and compound-related metabolites in skin, if conducted, will be reported under separate protocols and will be outside the scope of this statistical analysis plan.

Blood sample collection

Blood samples for PK analysis of GSK2981278 and related metabolite(s) will be collected at the time points indicated in section 2.3.1 and section 2.3.2, Time and Events Table. 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.

Plasma concentrations of GSK2981278 will be determined.

For **Part A**, if the concentration data permits, the following PK parameters will be calculated: AUC(0-t), Cmax, tmax, and steady state assessments such as $C\tau$ and time invariance.

Urine sample collection

Urine samples for analysis of GSK2981278 and related metabolite(s) will be collected at the timepoints listed in section 2.3.1, Time and events table. The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Total urine voided will be collected over the period of collection as specified in section 2.3.1.

Skin sample collection

Skin samples for evaluation of drug delivery will be collected in Part A, at Day 57 by taking a 4 mm punch biopsy from the area of psoriatic plaque identified for skin biopsies at baseline.

Skin biopsy samples for drug and metabolite analysis will be performed under the control of PTS-IVIVT-Bioimaging, GlaxoSmithKline. Skin biopsy samples may be analyzed for concentrations of GSK2981278 and compound-related metabolites using MALDI imaging or HPLC-MS and the results will be reported under a separate PTS-IVIVT-Bioimaging, GSK protocol. Raw data will be archived at GSK.

3.2.2 Pharmacodynamic variables

Skin samples for biomarker analyses will be collected at Baseline and Day 57 in Part A.

With the subject's consent, a total of 3 4-mm punch skin biopsies will be taken from each subject for biomarker analyses in Part A of this study: 1 from non-lesional skin at baseline, 1 from lesional skin at baseline and 1 at Day 57 from the treated skin of the same plaque where the baseline biopsy was taken. Skin sample(s) may be used for the purposes of measuring

novel biomarkers to identify factors that may influence psoriasis as well as the biological and clinical responses to GSK2981278.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with psoriasis and/or the action of GSK2981278 may be identified by application of:

- RNA transcriptome analysis of skin samples.
- Measurement of the levels of mRNA in skin samples.

RNA transcriptome analysis of skin samples

Transcriptome studies will be conducted using microarray, which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each skin sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to psoriasis or the action of GSK2981278.

Measurement of the levels of mRNA in skin samples

RNA expression studies will be conducted using quantitative RT-PCR technologies. The RNAs assayed will be those expected to be modulated by GSK2981278. These biomarkers include IL-17A, IL-17F, DEFB4A, IL-19, IL-36, CCL20, S100A7a, IL-8, IL-22, RORC and Krt6A. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to psoriasis or the action of GSK2981278.

The evaluation of the effect of GSK2981278 ointment on relevant biomarkers is out of scope of this SAP.

3.2.3 Efficacy variable(s)

All efficacy assessments should be performed by the same investigator or designated evaluator for an individual subject. In the event the same evaluator is not available for the duration of the study, another investigator or designated evaluator with comparable training will perform the assessments.

Target plaque severity score (TPSS)

A target lesion of at least 9 cm^2 with a TPSS ≥5 and an induration subscore ≥2 will be selected at baseline. The severity of erythema, scaling, and induration (plaque thickness) will be assessed by the investigator on a 5-point scale ranging from 0=none to 4=very marked:

Table 8 TPSS scales

Score	Scaling	Erythema	Induration
0 None	No evidence of scaling	No evidence of erythema; hyperpigmentation may be present	No elevation over normal skin
1 Slight	Occasional fine scale over less than 5% of the lesion	Faint erythema	Possible but difficult to ascertain whether there is a slight elevation above normal skin

Score	Scaling	Erythema	Induration
2 Moderate	Fine scales predominate	Light red coloration	Slight but definite elevation, typically edges are indistinct or sloped
3 Marked	Coarse scales predominate	Moderate red coloration	Moderate elevation with rough or sloped edges
4 Very marked	Very thick tenacious scale predominates	Dusky to deep red coloration	Very marked elevation typically with hard sharp edges

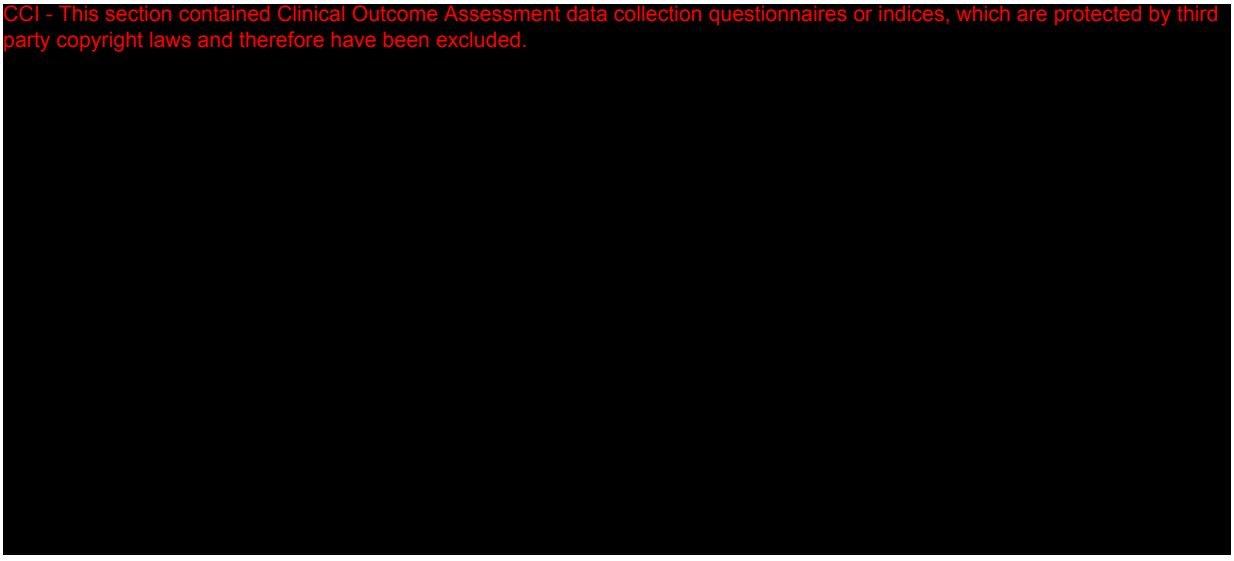
A total score will be calculated by adding the individual scores (13-point scale; maximum score 12). TPSS is the primary measure of clinical effect for this study.

Physician global assessment (PGA)

The PGA is a clinical tool for assessing the current state/severity of a subject's psoriasis. It is a static 5-point morphological assessment of overall disease severity, as determined by the investigator, using the clinical characteristics of erythema, plaque thickness, and scaling as guideline:

Table 9 PGA scale

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



At each specified time point, the PGA is made without reference to previous scores. Variations of the PGA are frequently used in clinical studies because it is a simple assessment that is more similar to the assessments actually used in clinical practice [Feldman, 2005]. PGA will be assessed on the entire treated area (i.e. including the scalp lesion, if applicable).

Psoriasis area and severity index (PASI)

The PASI scoring system is a widely-used standard clinical tool for assessing the severity of psoriasis that takes into account the overall severity of erythema (redness), thickness

(induration), and scale, as well as the extent of BSA affected with psoriasis [Feldman, 2005]. The 3 clinical signs are each graded on a 5-point scale (0 to 4) and the %BSA affected is scored on a 7-point scale (0-6) for each of the 4 specified body regions (head, upper extremities, trunk, and lower extremities).

Table 10 Elements of the Psoriasis Area and Severity Index

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Note: Items in shaded rows will be calculated from Items 1, 2, 3, and 5.

For Items 1, 2, and 3, generate an average score for erythema, thickness, and scale for each of the 4 body areas using the following 5-point scale: 0=None; 1=Slight; 2=Mild; 3=Moderate; 4=Severe. For Item 5, enter the area score for percentage of skin covered by psoriasis according to the following chart.

Table 11 Percentage of skin covered with psoriasis for each area

Area:	0%	1 - <10%	10 - <30%	30 - <50%	50 - <70%	70 - <90%	≥90%
Score:	0	1	2	3	4	5	6

The individual scores are multiplied by a weighted factor for each body region; the sum of these scores gives the overall PASI score. Higher scores indicate more severe disease. PASI is a static assessment made without reference to previous scores.

Body surface area (BSA)

The extent of BSA affected by psoriasis is a general indicator of disease severity and will be measured throughout the study. The extent of BSA to which study treatment is applied will also be recorded. It is suggested, for the purpose of approximate clinical estimation, the total palmar surface area of the palm plus five digits be assumed to be approximately equivalent to 1% BSA.

Assessment of body surface area with Psoriasis will be performed separately for four body surface regions: the head (h), the upper extremities (u), the trunk (t), and the lower extremities (l), corresponding to 10, 20, 30, and 40% of the total body area, respectively.

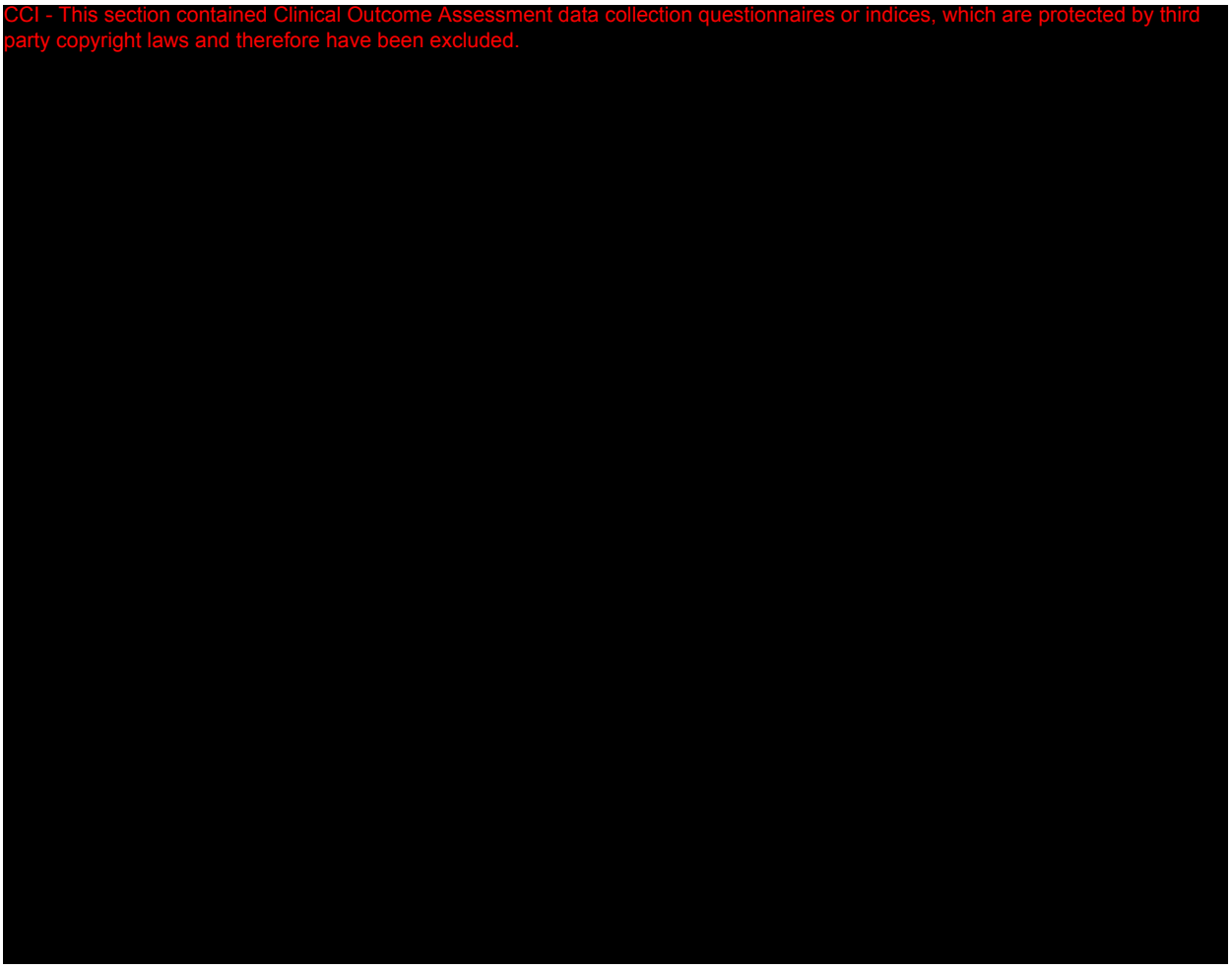
Table 12 Body region in percent of total body area

Body Region	Surface Area of Body Region
head (h)	10%
upper extremities (u)	20%
trunk (t)	30%
lower extremities (l)	40%

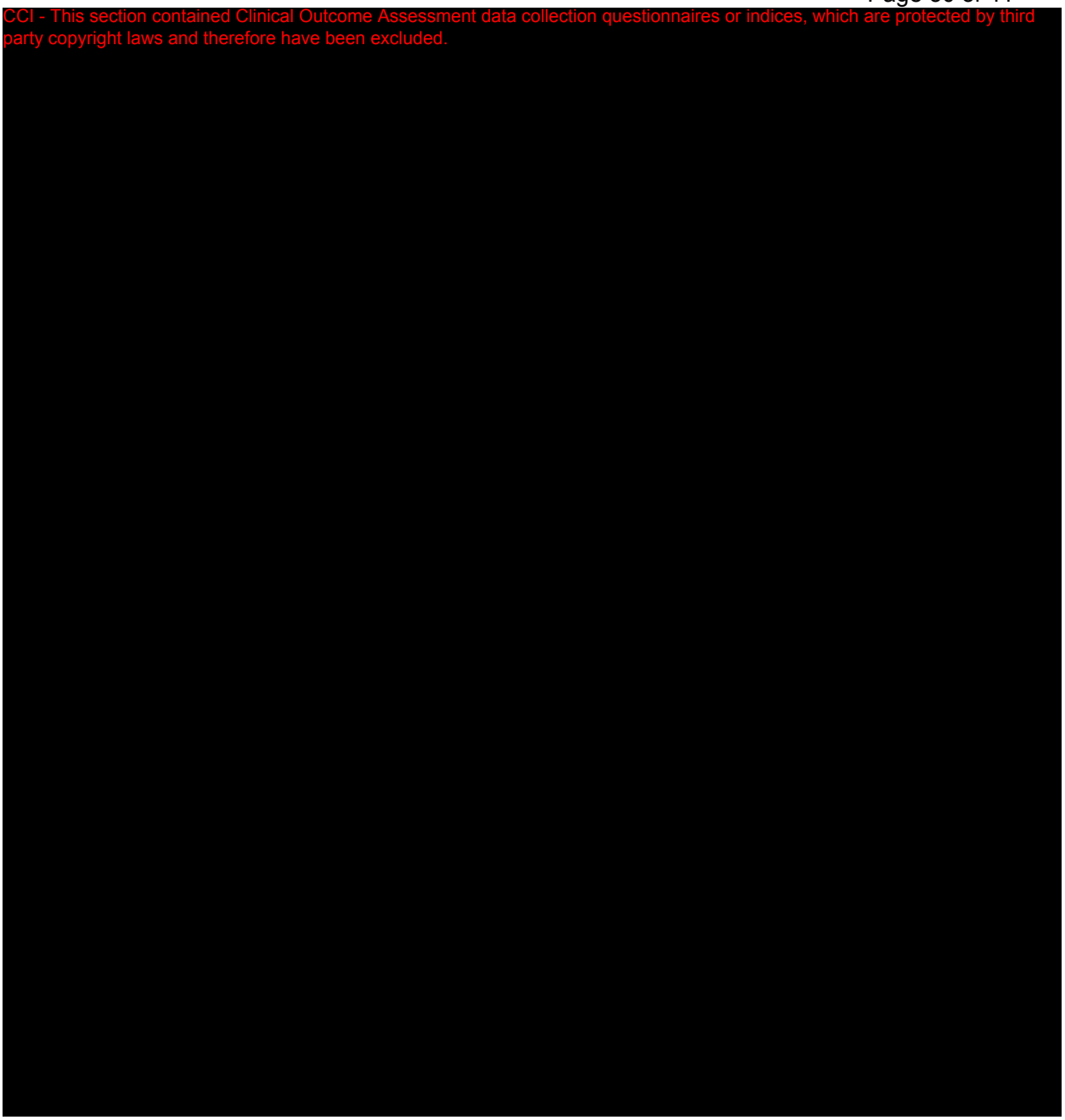
Psoriasis Symptom Diary

The Psoriasis Symptom Diary was developed to assess daily self-reports of psoriasis symptoms and the functional impact related to the underlying pathophysiology of the disease [Strober, 2013]. Questions about how severe and how bothersome various signs and symptoms are to the subject are answered using an 11-point numerical rating scale (see below). In this study, subjects will be asked to complete the Psoriasis Symptom Diary questionnaire at the clinic during the scheduled visits.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



3.2.4 Safety variables

Planned time points for all safety assessments are listed in the Time and events table (section 2.3.1 and section 2.3.2). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Safety will be assessed by the monitoring and recording of all AEs and SAEs; evaluation of application site tolerability; monitoring of hematology, clinical chemistry, urinalysis and vital signs; and the performance of ECGs and physical examinations.

Adverse events

The definitions of an AE or SAE can be found in CTP, Appendix 8.

- 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 (CTP, section 7.5.1.3), at the timepoints specified in the Time and Events Table (section 2.3.1 and section 2.3.2).
- 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.

Laboratory variables

All protocol required laboratory assessments, as defined in Table 13, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. 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.

All study-required laboratory assessments will be performed by a local laboratory, apart from liver events monitoring which will be performed by the central laboratory. The results of each test must be entered or electronically transferred into the eCRF.

Haematology, clinical chemistry, urinalysis and additional parameters are to be tested, as listed below.

Table 13 Laboratory Parameters

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]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate amino-transferase (AST) (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatise	Albumin

Laboratory Assessments	Parameters
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) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (at Screening for women of non-child bearing potential)
NOTES : Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in CTP, section 5.4.1 and CTP, Appendix 6.	

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.

Electrocardiogram (ECG)

Single 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 QTc intervals. QTcB will be utilized for this study. If QTcB is outside the threshold value of the eligibility criteria or stopping criteria, triplicate ECGs will be performed over a brief (e.g. 5 to 10 minutes) recording period with the QTcB values averaged. Refer to section 3.1 for QTc stopping criteria.

Application site tolerability

The investigator or designated evaluator will assess application site tolerability focusing on the treated non-lesional skin surrounding the plaques at each visit using the 5-point tolerability assessment scale presented in Table 14. Refer to section 3.1 for topical application site tolerability stopping criteria.

Table 14 Application site tolerability assessment scale

Grade	Severity	Description
0	None	No evidence of local intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking
3	Severe-To be reported as an AE	Erythema, edema glazing with fissures, few vesicles or papules: Remove and discontinue study treatment
4	Very Severe-To be reported as an AE	Strong reaction spreading beyond the treated area, bullous reaction, erosion: Remove and discontinue study treatment

Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until 2 weeks post-last dose.

Physical exams

A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen) and a measurement of weight. Height will be also measured and recorded at Screening.

Vital signs

Vital signs will be measured in seated or supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse 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.

3.3 Analysis populations

3.3.1 Efficacy population

Per Protocol (PP) analysis set will include all randomized subjects (in Part A, all randomized subjects refer to all subjects who are eligible for treatment phase as no randomization will take place), who comply closely with the protocol (e.g. have sufficient exposure).

The following deviations from the protocol are considered major for the exclusion of the subjects from the PP analysis set:

- violation of eligibility criteria;
- consumption of forbidden concomitant medication during the study;
- application of less than 80% or more than 120% of the planned number of 113 doses (see section 2.1);

Subjects will not be excluded from the PP, if the reason for the protocol deviation or premature treatment or trial discontinuation is due to lack of efficacy or due to an at least possibly treatment related adverse event.

Prior to breaking the blind and/or the data review meeting, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

PP analysis set will be the primary set for efficacy analyses.

3.3.2 Safety population

Safety analysis set will include all subjects exposed to at least 1 application of study product. The safety analysis set will be the primary set for safety analyses.

3.3.3 Pharmacokinetic population

Pharmacokinetic (PK) analysis set will include subjects with at least one sample collected and analyzed for plasma drug concentration. The PK analysis set will be the primary set for PK analyses.

3.3.4 Other populations

Screened analysis set will include all subjects who sign informed consent. This set will be used for evaluating screen failures, study populations and exclusion of subjects from any population.

Enrolled analysis set will include all subjects who are eligible for treatment phase, indicated by eligibility status eCRF page. This set will be used for evaluating subject disposition, reasons for study withdrawal, age ranges, planned and actual treatments.

3.4 Statistical methods

The statistical evaluation will be performed by bioskin using SAS® version 9.3 or higher (Statistical Analysis System, SAS Inc., Cary, NC) software package.

A complete set of raw data listings will be appended to the Statistical Report. All tables, figures and listings will be presented in RTF and PDF documents without any manual editing, i.e. they will appear unmodified as programmed by means of the statistical package.

Descriptive summaries will be given by treatment group and/or overall. The number of subjects within each treatment group of the analysis set will be given in each table.

Categorical variables will be summarized with counts (n) and percentages (%), together with the number of non-missing values. The number of non-missing values will be used as the denominator for the calculation of percentages. Incidence of adverse events will be based on the number of subjects in the respective analysis set and treatment group.

Descriptive statistics for continuous variables will be comprised of the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max), if not otherwise stated.

When applicable, these summaries will be provided by visit. In case of premature withdrawal from the trial, efficacy and safety assessments performed at the time point of withdrawal, will be summarized, separately to the planned visits.

As a rule, mean, and median will be reported to one decimal place more than the observed values, SD with two decimal places more than the observed values, Min and Max with the same number of decimal places as the observed values.

3.4.1 Discontinuations, dropouts and analysis populations

The number and percentage of subjects who entered, completed and withdrew during the whole study, as well as at the treatment period (Visit Day 1 to Visit Day 57) and the follow-up/end of study period (Follow-up Visit), together with reasons for discontinuation, will be tabulated for the enrolled analysis set. Screening status and reasons for screen failures will be tabulated for the screened analysis set. The number and percentage of subjects in each analysis set will be summarized with the screened analysis set.

Subjects discontinuing the study will be listed with date of discontinuation, study day of discontinuation, and reason for discontinuation. The reasons for screen failures will be listed with date of screen failure.

Important protocol deviations (section 3.3.1) will be listed with date of deviation, study day of deviation, as well as protocol deviation category, coded term and descriptions.

Subjects with inclusion/exclusion criteria deviations will be listed with inclusion/exclusion type and criteria descriptions.

Subjects enrolled but excluded from either PP analysis set, safety analysis set or PK analysis set will be listed along with date, study day and category of deviation, the criteria which lead to exclusion, as well as exclusion from populations.

3.4.2 Demographics and baseline characteristics

Demographic and background data, consisting of age (determined as number of full years of the difference between date of informed consent and date of birth, with day of birth set to June 30th), sex, race and ethnicity assessed at screening will be summarized using descriptive statistical methods for the enrolled analysis set. Baseline characteristics such as height [cm], and Fitzpatrick skin type will also be included in the summary.

Baseline assessments of efficacy and safety parameters will be presented in context of the evaluation of efficacy/safety parameters, with baseline, defined as the last observation prior to the first application of study treatment. Pregnancy tests and screening laboratory assessments will only be listed.

Past and current medical conditions, i.e. general medical history, cardiovascular events and history of stable plaque psoriasis, will be listed only. General medical history and cardiovascular events will be listed with classification and a flag identifying the condition as past or current, according to the definition in section 3.1.

Concomitant medications or therapies will be presented by GSKDrug Anatomical Therapeutic Chemical (ATC) classification level 1 (Body System) and ingredient. In any given category (e.g., drug category) a subject will be counted only once. Prior and concomitant medications/therapies will be listed.

Family history, as related to the inclusion/exclusion criteria will be listed only.

3.4.3 Treatment compliance

The treatment compliance will be assessed by evaluation of the total number of investigational medicinal product (IMP) applications and the % IMP applications.

The total number of IMP applications will be calculated by:

Duration of treatment [days] * 2 – 1 – number of missed applications + number of overdoses,

with duration of the treatment calculated by:

Date of last IMP application – Date of first IMP application + 1.

The % IMP applications will be calculated by (the total number of IMP applications / the planned total number of IMP applications) *100, where the planned total number of IMP application is 113 (see section 2.1).

The total number of IMP applications and % of IMP applications will be presented using descriptive statistics for continuous variables in the safety analysis set.

3.4.4 Efficacy analyses

3.4.4.1 Hypotheses

No formal hypothesis tests are planned. Descriptive statistics will be used to assess the key objectives of this study: evaluation of safety, tolerability, systemic exposure and clinical effect of topically applied GSK2981278 ointment in subjects with plaque psoriasis.

3.4.4.2 Statistical analyses

Clinical effect data will be summarized using both the Observed Cases (OC) approach and the last observation carried forward (LOCF) approach if there are missing values.

Both change and percent change in TPSS, PGA, PASI and Psoriasis Symptom Diary scores, and in %BSA affected and treated, from baseline to each study visit will be summarized based on the per protocol analysis set. For TPSS, the individual subscore for scaling, erythema and induration, as well as the total score will be summarized. For PASI, the item 6 score for each body area, as well as the total score will be summarized. For Psoriasis Symptom Diary, the score for severity of itching (Question 1), the score for bother of itching (Question 2) and the total score, calculated by the sum of scores from each question, will be summarized. The mean Total TPSS score will be presented by a line plot.

3.4.5 Safety analyses

Safety will be evaluated by extent of exposure to study drug, adverse events (AEs), application site tolerability, lab data and vital signs.

3.4.5.1 Extent of exposure to study drug

The extent of exposure to study drug will be summarized by the duration of the treatment, the total number of IMP applications, the total amount of IMP used [g] and the average amount of IMP used per application [g]. For each treatment descriptive statistics will be presented in the safety analysis set.

The duration of the treatment and total number of IMP applications will be calculated, as given in section 3.4.3. Total amount of IMP used [g] will be determined from the weights of distributed and returned IMP containers and average amount per application [g] will be calculated as the total amount of IMP used divided by the total number of IMP applications.

The exposure to study treatment will be summarized. A by-subject listing of data on subject exposure to study treatment will also be produced with start date/time, end date/time, duration

of the treatment, dose, dose units, dose formulation, dose frequency, the total number of IMP applications, the total amount of IMP used [g], the average amount of IMP used per application [g], and % of IMP applications.

3.4.5.2 Adverse events

AEs will be coded according to version 20.0 of medical dictionary for regulatory activities (MedDRA). If data allow, summaries of AE will be provided. Frequencies and percentages will be presented overall, for each system organ class, and for each preferred term. Summaries of treatment-emergent AEs, treatment-related AEs, AEs leading to discontinuation of study treatment, and SAEs will be provided. When appropriate, AE onset date, end date, duration [days] (end date – onset date + 1), time since study treatment start date [days] (onset date - study treatment start date + 1), seriousness, severity, relationship to study drug, action taken, and outcome will be listed by subject together with baseline characteristics including age, race, sex, weight and BMI.

3.4.5.3 Laboratory analyses

Change from baseline in hematology and chemistry results will be summarized at every scheduled time point. Urinalysis dipstick results will be summarized by frequency counts. The number of subjects with abnormal values based on values relative to the laboratory normal ranges will be summarized for each assessed time point.

A listing of all laboratory data for subjects with any value of PCI or outside the normal range and a listing of laboratory values of PCI or outside the normal range will be provided. A listing of laboratory data with character results will be provided. When appropriate, the listing will include age, race, sex, the laboratory test name (units), planned visit, date of lab sample, study day of lab sample, lab test value, normal value range, abnormal range flag, and PCI flag.

A listing of urinalysis data for subjects with any value of PCI will be provided.

3.4.5.4 ECG analyses

Change from baseline at every scheduled time point for each ECG parameter will be summarized using descriptive statistics. The ECG will be evaluated by the investigator as “Normal”, “Abnormal, not clinically significant”, and “Abnormal, clinically significant”. A summary of ECG findings will be provided. Also, a listing of all ECG data for subjects with any value of PCI, a listing of ECG values of PCI and a listing of ECG clinically significant abnormal findings will be generated.

3.4.5.5 Tolerability analyses

A listing of application site tolerability will be provided.

3.4.5.6 Other safety analyses

Change from baseline for each vital sign parameter, including weight [kg] and the body mass index (BMI) [kg/m²], determined as weight [kg] / (height [m])^2, will be summarized by visit using descriptive statistics. A listing of vital signs and a listing of change from baseline for vital signs will be provided. A listing of vital signs for subjects with any value of PCI and a listing of vital signs of PCI will be provided.

If applicable, liver event data will be listed.

3.4.6 Pharmacokinetic analyses

3.4.6.1 Overview of planned pharmacokinetic analyses

The Pharmacokinetic analyses will be based on the "Pharmacokinetic" population, unless otherwise specified. Derivation of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline.

Table 15 provides an overview of the planned Pharmacokinetic analyses:

Table 15 Overview of Planned Pharmacokinetic Analyses

[Endpoint / Parameter/ Display Type]	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK Concentrations														
Plasma GSK2981278 concentrations				Y	Y	Y	Y					Y	Y	
PK Parameters														
Plasma GSK2981278 parameters				Y			Y				Y		Y	

NOTES :
- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

3.4.6.2 Drug Concentration Measures

Concentrations of GSK2981278 in plasma will be listed and summarized by visit (Day 1, Day 15, Day 29, Day 57) and nominal time. Standard summary statistics will be calculated. Refer to the guidance document, Non-Compartmental Analysis of Pharmacokinetic Data [GUI_51487], for more information regarding the treatment of GSK2981278 concentrations below the assay's lower limit of quantification (NQ).

3.4.6.3 Pharmacokinetic Parameters

3.4.6.3.1 Deriving Pharmacokinetic Parameters

- The pharmacokinetic parameters in plasma will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin v 6.3 or higher.
- All calculations of non-compartmental parameters will be based on actual sampling times for the final analysis.

Pharmacokinetic parameters described in
Table 16 will be determined from the plasma concentration-time data, as data permits. All parameters will be calculated for Day 1, 29 and Day 57 as data permits, except where stated otherwise for time-invariance.

Table 16 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
AUC(0-t)	Area under the concentration-time curve from time zero to the last measured concentration [10 hrs] will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Time-invariance	Time-invariance estimated as a ratio of AUC(0-t) on Day n (where n=29, 57) to AUC(0-t) on Day 1.

NOTES:

- Additional parameters may be included as required.

3.4.6.3.2 Statistical Analysis of Pharmacokinetic Parameters

No planned statistical analyses of pharmacokinetic parameters. Pharmacokinetic parameters will be summarized descriptively. Log10-transformed data will be summarized by the geometric mean, determined as 10 to the power of the mean of log-transformed data, standard deviation of log10-transformed data (SD(log)), and the between subject coefficient of variation (%CVb), determined as

$$\sqrt{10^{(\mathrm{SD}(\log))^2} - 1} * 100.$$

3.5 Data handling conventions

- For this study subject data will be entered into GSK/bioskin defined eCRFs, 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) Version 20.0 and an internal validated medication dictionary, GSKDrug Version 1.3.
- eCRFs (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.

3.5.1 Missing data

A description of missing data will be provided in the clinical study report.

Clinical effect data will be summarized using both the Observed Cases (OC) approach and the last observation carried forward (LOCF) approach if there are missing values. Only efficacy data up to Day 57 visit will be imputed. No imputation for the Follow-up visit will be carried out.

For past and current medical conditions, missing or incomplete (i.e., partial missing) start date and/or stop date will not be imputed. If the stop date is not identifiable as prior to date of first application of study treatment, the medical condition will be considered as current, and past, otherwise (see section 3.1).

For prior or concomitant medications or therapies, incomplete (i.e., partial missing) start date and/or stop date will not be imputed. If the stop date is not identifiable as prior to date of first application of study treatment, the medication or therapy will be considered as concomitant, and prior, otherwise (see section 3.1).

For the assessment of order of events, event A is prior to event B, if year of event A is prior of year of event B, or if years are equal, if month of event A is prior to month of event B, or if years and months are equal, if day of event A is prior to day of event B.

3.5.2 Window for time points

Visit window violations will be documented as protocol deviations and assessed within the blind data review meeting.

Assessments performed out of the planned visit windows will be assigned to the nearest, directly preceding or following, planned visit, only, if the visit is missing. If both visits are missing and the distances are equal, the assignment is performed to the following one. Otherwise the assessments will not be included in the statistical evaluation and will be listed only.

3.5.3 Unscheduled visits

If applicable, the reason for unscheduled visit measurements will be given together with the results in data listings. For the analysis, the unscheduled assessments will be assigned to a planned visit following the procedure in section 3.5.2, above.

3.5.4 Pooling of centers for statistical analyses

Not applicable.

3.5.5 Statistical technical issues

Not applicable.

3.5.6 Database related issues

Not applicable.

4 Interim analysis

No formal interim analysis is planned.

5 Software documentation

The statistical evaluation will be performed at bioskin using the software package SAS (Statistical Analysis System, SAS Inc., Cary, NC).

6 References

GlaxoSmithKline Document Number 2016N275350_01 Study ID 203820. A two-part trial to evaluate the safety, tolerability, clinical effect and systemic exposure potential of topically applied GSK2981278 ointment in subjects with plaque psoriasis. 2016-Dec-13.

Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis. 2005;64:65-68.

GlaxoSmithKline Document Number GUI_51487, version 4.0. Non-compartmental analysis of pharmacokinetic data. Effective date 2014-Oct-29.

Lebwohl, M. AMAGINE-2: A Randomized, Double-blind, Phase 3 Efficacy and Safety Study of Brodalumab Compared With Placebo and Ustekinumab in Moderate to Severe Plaque Psoriasis Patients. AAD 2015 Late-breaking abstract F010.

Strober BE, Nyirady J, Mallya UG, Guettner A, Papavassilis C, Gottlieb AB. Item-level psychometric properties for a new patient reported Psoriasis Symptom Diary. Value Health. 2013;16:1014-1022