Statistical Analysis Plan

Sponsor Name:	Ziarco Pharma Ltd
Protocol Number:	ZPL521/101 / NCT02795832
Protocol Title:	A Randomised, Adaptive Design, Double-Blind (3rd Party Open), Placebo Controlled, Sequential Group Study To Determine The Safety, Tolerability, Pharmacokinetics And Efficacy Of Twice Daily Application Of A Topical ZPL-5212372 (1.0% W/W) Ointment Administered For Up To 2 Weeks In Adult Healthy Volunteers And Patients With Moderate To Severe Atopic Dermatitis
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SAP Version Date:	16th March 2017

Signature Page

Protocol Number:	ZPL521/101
Protocol Title:	A randomised, adaptive design, double-blind (3rd party open), placebo controlled, sequential group study to determine the safety, tolerability, pharmacokinetics and efficacy of twice daily application of a topical ZPL-5212372 (1.0% w/w) ointment administered for up to 2 weeks in adult healthy volunteers and patients with moderate to severe atopic dermatitis
Version:	Final v2.0
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I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AD	Atopic Dermatitis
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Curve
BLQ	Below Limit of Quantification
BSA	Body Surface Area
CI	Confidence Interval
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of Variation
EASI	Eczema Area and Severity Index
ECG	Electrocardiograms
FAS	Full Analysis Set
IGA	Investigator Global Assessment
IMP	Investigational Medicinal Product
IWRS	Integrated Web-based Response System
LOQ	Limit of Quantification
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
LS	Least Square
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
QTcF	Heart Rate Corrected QT interval, using Fridericia's formula
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PP	Per Protocol

Abbreviation	Description
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
[redacted]	[redacted]
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
VRS	Verbal Rating Score
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. Any amendments to the SAP will be made prior to database lock. Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report (CSR).

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings (TFLs). Pharmacokinetic (PK) parameters will be derived by [redacted] and provided to [redacted] for presentation.

3. STUDY OVERVIEW

3.1. STUDY OBJECTIVES

3.1.1. Primary Objectives

Cohorts 1 and 2
To assess the safety and tolerability, local and systemic, of ZPL-5212372 administered as a topical ointment (containing 1.0% [w/w] concentration of ZPL-5212372) twice daily, for 1 week, to healthy subjects and patients with moderate to severe atopic dermatitis (AD).

Cohort 3
To evaluate the efficacy of ZPL-5212372 administered as a topical ointment (containing 1.0% [w/w] concentration of ZPL-5212372) twice daily, for 2 weeks, to patients with moderate to severe AD.

3.1.2. Secondary Objectives

Cohorts 1 and 2
To investigate the systemic pharmacokinetics of ZPL-5212372 following single and multiple dose topical applications of a 1.0% [w/w] concentration of ZPL-5212372 ointment, administered twice daily, for 1 week, to healthy subjects and patients with moderate to severe AD.

Cohort 3
To assess the safety and tolerability, local and systemic, of ZPL-5212372 administered as a topical ointment (containing 1.0% [w/w] concentration of ZPL-5212372) twice daily, for 2 weeks, to patients with moderate to severe AD.

To investigate the trough concentrations of ZPL-5212372 in patients with moderate to severe AD

following twice daily applications of ZPL-5212372 administered as a topical ointment (containing 1.0% [w/w] concentration of ZPL-5212372).

3.1.3. Exploratory Objectives

Cohorts 1 to 3
To explore the subject's perception of the Ziarco development ointment formulation using the Ziarco Ointment Questionnaire.

3.2. STUDY DESIGN

This is a randomised, adaptive design, double-blind (3rd party open), placebo controlled, sequential group study in adult healthy volunteers and in patients with moderate to severe AD.

The study consists of 3 sequential cohorts each separated by formal safety reviews conducted by the Safety Review Team. The study will recruit cohorts sequentially and use sentinel subjects (n=3) in Cohorts 1 and 2 to minimize the risk to subjects and make it possible to modify specific features of the study dependent on emerging data; however the flexibility of the adaptive features will be constrained by clear boundaries/stopping criteria (refer to Protocol Sections 3.2 and 3.7). The main features of each cohort are summarised in Table 1 below:

Table 1: Overview of Cohorts

	Cohort 1	Cohort 2	Cohort 3
Subject Population	Healthy adults	Moderate to severe AD patients	Moderate to severe AD patients
In-patients/Out-patients	In-patients	In-patients	Out-patients
Total Number of subjects	12	12	30
Ratio Active:Placebo	2:1	2:1	2:1
Dosing Duration	7 days	7 days	14 days
Follow-up Visit (after last dose of study medication)	7-14 days	7-14 days	7-14 days

Progression from Cohort 1 to Cohort 3 will be dependent on the demonstration of adequate safety within the protocol defined boundaries. In Cohorts 1 and 2, complete data sets from a minimum of 4 active and 2 placebo subjects with 40% body surface area (BSA) treated with study ointment will need to be reviewed by the Safety Review Team in order to decide whether to proceed as planned to the next cohort. In the event that it is decided not to proceed to the next cohort, the reviewers may decide to:

- modify the study within the boundaries of the adaptive features and continue,

- to submit a substantial protocol amendment, or
- suspend the study.

In addition, in order to ensure subject safety, Cohorts 1 and 2 will be split to have an initial sentinel group which will precede the remaining subjects in the cohort. The sentinel group will consist of 3 subjects (2:1 Active to Placebo) and these subjects will be dosed twice daily, to cover 10% BSA with study ointments for 7 days. Provided that the study ointment is well tolerated after 48 hours (i.e. 4 applications) the remainder of the cohort (9 subjects; 2:1 Active to Placebo) may start dosing with coverage of 40% BSA BID for 7 days. Cohort 3 will have AD affected skin dosed to a maximum of 50% BSA.

All subjects will have a screening visit to confirm suitability to enter the study, within 28 days of Day 1 (first day of dosing). AD patients in Cohorts 2 and 3 will be required to switch from their usual emollient to using the study emollient twice daily for at least 7 days prior to Day 1 and throughout their participation in the study. Dosing will commence on Day 1 and continue for 7 or 14 days, depending on which cohort subjects are allocated to. Subjects in Cohorts 1 and 2 will remain in the clinical research unit (CRU) until Day 9 (48 hours after the last application of study ointment). Subjects in Cohort 3 will have their first application of ointment in the unit and continue dosing at home, returning to the unit for assessments on Days 5, 8, 10 and 15 (after the last ointment application at home on the evening of Day 14).

All subjects will be required to attend the CRU for a follow-up visit 7-14 days after the last application of study ointment. AD patients may recommence use with other topical or systemic treatments for their AD, if required, from either discharge from the CRU (Cohort 2) or the end of dosing (Cohort 3).

3.3. DETERMINATION OF SAMPLE SIZE

The sample sizes for Cohorts 1 and 2 are not based on formal statistical testing. Their sample sizes are considered sufficient to obtain suitable safety, tolerability and PK data prior to starting Cohort 3.

For Cohort 3 the sample size of 30 subjects has been determined on the basis of comparing the mean ZPL-5212372 Week 2 percentage change from baseline in the Eczema Area and Severity Index (EASI) score to that for placebo. With 20 subjects in the ZPL-5212372 group and 10 subjects in the placebo group, there is 80% power of obtaining a statistically significant result, assuming that there is an improvement of at least 30% with ZPL-5212372 compared to placebo and a standard deviation for the percentage changes from baseline between subjects of 30%. This is based on the analyses described and a 1-sided test at the 5% level of significance.

3.4. TREATMENT ASSIGNMENT AND BLINDING

Upon screening, each subject will receive a 3-digit number, by the Integrated Web-based Response System (IWRS), which will be used throughout the study. Screened subjects who drop out of the study before randomisation will retain their number.

Subjects will be randomised on a 2:1 basis to topical ZPL-5212372 or placebo, twice daily. For the randomisation of subjects, the investigator will use the IWRS. The IWRS will use a computer-generated randomisation schedule to assign subjects to treatment. In Cohort 3 subjects will be stratified by baseline EASI score (≤20 and >20), to ensure an even distribution of severities across both treatment groups.

The study is double-blind third party open i.e. the study will be subject- and investigator-blinded. Details of personnel who will be able to review unblinded subjects' data during the study will be held in a separate document by Ziarco.

The study blind should not be broken except in a medical emergency, where knowledge of the study drug received would affect the treatment of the emergency, or obtaining this information is a regulatory requirement. If time permits, the investigator should notify the Sponsor prior to contacting IWRS. All calls resulting in an unblinding event will be reported by the IWRS to the Sponsor. If the blind is broken, the date, time and reason will be recorded in the subject's CRF.

3.5. ADMINISTRATION OF STUDY MEDICATION

Subjects in Cohorts 1 and 2 will have twice daily topical applications of either 1.0% (w/w) ZPL-5212372 ointment or matching placebo ointment approximately 12 hours apart. The morning dose will be administered between 07:00 to 10:00 hours and the evening dose approximately 12 hours later between 19:00 – 22:00 hours. Study ointment will be dispensed from the pharmacy (one jar per subject) to clinical staff. Clinical staff will consult the subject's body map to confirm whether 10 or 40% BSA will have application of ointment. For 10% BSA approximately [redacted] and for 40% BSA approximately [redacted] by clinic staff at the subject's bedside. If the initial volume of ointment is inadequate to cover the dosing area, additional ointment may be applied up to a maximum of 1 mL/2% BSA (i.e. 5 mL for 10% BSA or 20 mL for 40% BSA).

Subjects in Cohort 3 will apply twice daily (approximately 12 hours apart) applications of either 1.0% (w/w) ZPL-5212372 ointment or matching placebo ointment at home. At the randomisation visit the extent of their AD will be assessed and a recommended amount (approximately 1.25 to 5 mL/10% BSA) of ointment for use on their AD affected skin will be recorded on their individual body map. Subjects will be instructed not to use ointment on non-AD affected skin. Study ointment will be dispensed from the pharmacy (three jars per subject) to clinical staff. The first application of study ointment will be applied by the subject in the clinic under the supervision and direction of the clinical staff i.e. the amount to apply, body area to cover using the body map as a guide and how to draw up the correct amount of study ointment [redacted] will be explained, as this will vary from subject to subject.

<u>Emollients</u>
The emollient [redacted] will be supplied for this study for AD subjects in Cohorts 2 and 3. In addition an alternate emollient will be available for Cohort 3 subjects who have a potential for

any hypersensitivity skin reactions to [redacted] (Protocol version 2.0). Any emollients and bathing products used by the subject should be documented at screening. Subject emollients may be used up until 7 days prior to Day 1 and then subjects must stop using their current emollient and switch to using the study emollient in the same manner as their previous emollient. From randomisation subjects must use study emollient at least 15 minutes after application of study ointment. Subjects should use study emollient on all AD affected skin areas which have not been treated with study ointment and in addition any areas which the subject would treat as part of their normal skin care routine (Protocol Section 3.2 Table 2 adaptive feature). Cohort 2 subjects must continue using study emollient twice daily until discharge from the CRU on Day 9 and Cohort 3 subjects must use study emollient twice daily until they have completed their visit on Day 15.

Shower Cream

[redacted]
subjects, for use when showering each morning whilst resident in the CRU.

3.6. STUDY FLOWCHART

Schedule of Activities For Cohort 1 (Healthy Volunteers)

Activities	Screening[1]	Day 1	Day 2 to Day 6	Day 7	Day 8	Day 9/ Early Termination	Follow up 7-14 days post last dose
In-patient in CRU		X[2]----------X					
Informed Consent	X						
Demographics	X						
Medical history	X	X[3]					
Physical exam[4] (inc ht/wt)	X	X				X	X
12-lead ECG[5]	X	X	X	X	X	X	X
Vital signs (BP and PR)[6]	X	X	X	X	X	X	X
Breath alcohol and drug screen	X	X					
Pregnancy Test[7]	X	X					X
Serum FSH[8]	X						
Safety labs (inc urinalysis)	X	X[9]	X[10]			X	X
Hepatitis B/C, HbA1c, HIV	X						
Fitzpatrick skin type assessment	X						
Body Map Recorded		X					
PK blood sample[11]		X	X	X	X	X	
Assessment of local toleration[12]		X	X	X	X	X	
Ointment Questionnaire					X		
Randomisation		X					
Dosing[13]		X----------X					
Concomitant & prior medications	X----------X						
AE collection and review[14]	X----------X						

1 Screening may occur over more than 1 day.
2 Subjects may come into the CRU on the evening before and some pre-dose activities may be completed.
3 Review changes in the subject's medical history since screening.
4 Full Physical examination at Screening, a brief examination on all other occasions (guided by AEs, but to include, as a minimum, general appearance, heart, lungs and skin).
5 Single ECG assessments at screening, follow up and early termination (if applicable). Triplicate ECG assessments will be performed at pre-dose, 1, 2, 4, 8, 12, 13 (Day 1 only) and 24 hours post-morning dose on Day 1 and Day 7, prior to each dose on Days 2 to 6, and at 36 hours (Day 8) and at 48 hours (Day 9) post last dose.
6 Duplicate, supine only, vital sign assessments will be performed at Screening, pre-dose, 1, 2, 4, 8, 12, 13 (Day 1 only) and 24 hours post-morning dose on Day 1 and Day 7, prior to each dose on Days 2 to 6, and at 36 hours (Day 8) and at 48 hours (Day 9) post last dose, follow up and at early termination (if applicable).
7 Serum pregnancy test at Screening, urine at all other specified time points; for women of child-bearing potential only.
8 Serum FSH testing for post-menopausal females 45-60 years only.
9 An additional blood sample will be taken at Baseline and stored frozen at MAC, as a reference sample, in case extra tests are required.
10 An additional safety lab sample will be taken on Day 4.
11 Blood samples for analysis of ZPL-5212372 will be taken prior to dosing and at 1, 2, 4, 8, 12, 13 (Day 1 only), 16 and 24 hours post-morning dose on Day 1 and Day 7, prior to each dose on Days 2 to 6, and at 36 hours (Day 8) and at 48 hours (Day 9) post last dose.
12 Assessment of local toleration on treated skin will be conducted prior to each dosing occasion and at 24 and 48 hours post last dose.
13 Dosing twice daily, 12 hours apart from Days 1 to 6, the last application of study medication will be the morning of Day 7.
14 Adverse events will be collected from the signing of the consent form until the follow up visit. SAE's collected up to 30 days post last dose.

Schedule of Activities For Cohort 2 (Moderate To Severe AD Patients)

Activities	Screening[1]	Washout Period[2]	Day 1	Day 2 to Day 6	Day 7	Day 8	Day 9/ Early Termination	Follow up 7-14 days post last dose
In-patient in CRU			X[3]----------	----------	----------	----------	----------X	
Informed Consent	X							
Demographics	X							
Medical history	X		X[4]					
Physical exam[5] (incl ht/wt)	X		X				X	X
12-lead ECG[6]	X		X		X		X	X
Vital signs (BP and PR)[7]	X		X	X	X	X	X	X
Breath alcohol and drug screen	X		X					
Pregnancy Test[8]	X		X					X
Serum FSH[9]	X							
Safety labs (inc urinalysis)	X		X[10]	X[11]			X	X
Hepatitis B/C, HbA1c, HIV	X							
Fitzpatrick skin type assessment	X							
Study emollient use[12]		X----------	----------	----------	----------	----------	----------X	
Body Map Recorded			X					
PK blood sample[13]			X	X	X	X	X	
EASI/IGA/BSA[14]	X		X		X			X
Ointment Questionnaire						X		
Randomisation			X					
Dosing[15]			X----------	----------	----------X			
Concomitant & prior medications	X----------	----------	----------	----------	----------	----------	----------	----------X
AE collection and review[16]	X----------	----------	----------	----------	----------	----------	----------	----------X

1 Screening may occur over more than 1 day.
2 Washout period from AD medication of between 1 week and 1 month dependent on each patient's current AD medication. Study Emollient should be started 7 days before Day 1.
3 Patients may come into the CRU on the evening before and some pre-dose activities may be completed.
4 Review changes in the subject's medical history since screening.
5 Full Physical examination at Screening, a brief examination on all other occasions (guided by AEs, but to include, as a minimum, general appearance, heart, lungs and skin).
6 Single ECG assessment at screening, follow up and early termination (if applicable). Triplicate ECG assessments will be performed at pre-dose, 1, 2, 4, 8, 12, 13 (Day 1 only) and 24 hours post-morning dose on Day 1 and Day 7.
7 Duplicate, supine only, vital sign assessments will be performed at Screening, pre-dose, 1, 2, 4, 8, 12, 13 (Day 1 only) and 24 hours post-morning dose on Day 1 and Day 7, prior to each dose on Days 2 to 6, and at 36 hours (Day 8) and at 48 hours (Day 9) post last dose and at follow up.
8 Serum pregnancy test at Screening, urine at all other specified time points; for women of child-bearing potential only.
9 Serum FSH testing for post-menopausal females 45-60 years only.
10 An additional blood sample will be taken at Baseline and stored frozen at the MAC, as a reference sample, in case extra tests are required.
11 An additional safety lab sample will be taken on Day 4.
12 Study emollient to be used from day -7 onwards until discharge from the CRU on day 9.
13 Blood samples for analysis of ZPL-5212372 will be taken prior to dosing and at 1, 2, 4, 8, 12, 13 (Day 1 only), 16 and 24 hours post-morning dose on Day 1 and Day 7, prior to each dose on Days 2 to 6, and at 36 hours (Day 8) and at 48 hours (Day 9) post last dose.

14 EASI/IGA/BSA assessed at screening and prior to randomisation to ensure inclusion criteria are met. Assessed again at the end of the study (or early termination) to document severity and extent of AD following study medication.

15 Dosing twice daily, 12 hours apart from Days 1 to 6, the last application of study medication will be the morning of Day 7.

16 Adverse events will be collected from the signing of the consent form until the follow up visit. SAE's collected up to 30 days post last dose.

Schedule of Activities For Cohort 3 (Moderate To Severe AD Patients)

Activities	Screening[1]	Washout Period[2]	Baseline Visit 1 (Day 1)	Visit 2 (Day 5)	Visit 3 (Day 8)	Visit 4 (Day 10)	Visit 5 (Day 15)/ Early Termination	Follow up 7-14 days post last dose
Informed Consent	X							
Demographics	X							
Medical history	X		X[3]					
Physical exam[4] (incl ht/wt)	X		X				X	X
12-lead ECG[5]	X							X
Vital signs (BP and PR)[6]	X		X	X	X	X	X	X
Breath alcohol and drug screen	X		X					
Pregnancy Test[7]	X		X				X	X
Serum FSH[8]	X							
Safety labs (inc urinalysis)	X		X[9]				X	X
Hepatitis B/C, HbA1c, HIV	X							
Fitzpatrick skin type assessment	X							
Study emollient use[10]		X----------					----------X	
Body Map Recorded			X					
PK blood sample[11]			X	X	X	X	X	
EASI/BSA/IGA	X		X	X	X	X	X	X
Ziarco Itch Questionnaire[12]			X	X	X	X	X	X
PGIC							X	
Ointment Questionnaire							X	
Randomisation			X					
Dosing[13]			X----------			----------X		
Concomitant & prior medications		X----------						----------X
AE collection and review[14]		X----------						----------X

1. Screening may occur over more than 1 day.
2. Washout period from AD medication of between 1 week and 1 month dependent on each patient's current AD medication. Study Emollient should be started 7 days before Day 1.
3. Review changes in the patient's medical history since screening.
4. Full Physical examination at Screening, a brief examination at all other visits (guided by AEs, but to include, as a minimum, general appearance, heart, lungs and skin).
5. A triplicate ECG assessment will be performed at Screening and a single ECG at Follow Up.
6. Duplicate, supine only, vital sign assessments to be performed at Screening and pre-dose on days 1, 5, 8, 10, 15 and follow-up.
7. Serum pregnancy test at Screening, urine at all other specified time points; for women of child-bearing potential only.
8. Serum FSH testing for post-menopausal females 45-60 years only.
9. An additional blood sample will be taken at Baseline and stored frozen at the central lab, as a reference sample, in case extra tests are required.
10. Study emollient to be used from day -7 onwards until completion of visit on day 15.
11. Blood samples for analysis of ZPL-5212372 will be taken prior to dosing on days 1, 5, 8 and 10 and an approximately 12 hours post last dose sample will be taken on Day 15.
12. Pruritus NRS, VRS, duration and impact of itch on sleep disturbance for the previous 24 hour period at clinic visits (Days 1, 5, 8, 10 and 15) by clinical staff asking the patients to complete the Ziarco Itch Questionnaire (Appendix 9).
13. To be dosed topically twice daily at home except on study visit days when the morning dose will be applied in the clinic after all other study assessments have been completed. Medication should be applied in the morning (preferably after showering) and approximately 12 hours later in the evening. Study medication should be applied approximately 15 minutes prior to using the Study Emollient. Subjects will apply their last dose of study medication at home in the evening of day 14 prior to their visit to the clinic on day 15.
14. Adverse events will be collected from the signing of the consent form until the follow up visit. SAE's collected up to 30 days post last dose.

4. ENDPOINTS

As Cohort 1 includes healthy volunteers no efficacy data will be collected. Though some efficacy assessments are included for Cohort 2 the data will only be listed and no formal comparisons will be made between the treatment groups. Consequently efficacy endpoints will only be assessed for Cohort 3.

4.1. PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint for Cohort 3 is the percentage change from baseline to Week 2 in the EASI score.

The EASI is a validated tool used to measure the severity and extent of atopic eczema (refer to Protocol Appendix 11 – EASI for descriptions of the ratings and the algorithm used to calculate the EASI score). The total score incorporates the extent of body regions affected and the intensity of a representative area of eczema. The approximate percentages affected by eczema are calculated for each region. A higher score indicates more severe disease.

EASI is assessed at all visits for Cohorts 2 and 3, and must be ≥9 and ≤48 at screening and ≥12 and ≤48 on Day 1 for the patient to be eligible for inclusion in the study.

4.2. SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints for Cohort 3 are:

EASI-50
EASI-50 response (yes/no). This is defined as a ≥50% reduction from baseline in EASI score at Week 2.

EASI-75
EASI-75 response (yes/no). This is defined as a ≥75% reduction from baseline in EASI score at Week 2.

EASI Components
A score for the EASI components (erythema [E], oedema/papulation [O], excoriation [X] and lichenification [L]) will be calculated across the body regions in a similar way to the calculation of the EASI total score. For example:

$$\text{Erythema}=[0.1\text{x}E_{head}\text{x}\text{Extent}_{head}]+[0.2\text{x}E_{arms}\text{x}\text{Extent}_{arms}]+[0.3\text{x}E_{trunk}\text{x}\text{Extent}_{trunk}]+[0.4\text{x}E_{legs}\text{x}\text{Extent}_{legs}]$$

The secondary endpoints associated with Cohort 3 are percentage change from baseline for each of the EASI components (erythema, oedema/papulation, excoriation and lichenification).

Investigator Global Assessment (IGA)
An overall assessment of the severity of AD will be made, by the investigator, using the IGA at

each visit for Cohorts 2 and 3. IGA scores take values on a 5-point scale from 0-4, where 0=clear to 4=severe disease. At screening and Day 1 IGA must be ≥ 3 for the subject to be eligible.

The following secondary endpoints will be assessed for IGA for Cohort 3:

- A subject will be considered as having IGA success if they achieve a score of 'Clear' or 'Almost clear'; note, as subjects require a score of ≥ 3 to enter the study they must have a reduction of ≥ 2 from baseline to achieve success
- A subject will be considered as having an IGA response if they achieve a score of 'Clear' or 'Almost clear', or a reduction of ≥ 2 from baseline

Numerical Rating Scale (NRS)

The Pruritus NRS is an assessment tool that will be used to assess the subject's worst itch as a result of AD in the previous 24 hours. Subjects in Cohort 3 will be required to complete the Ziarco Itch questionnaire at each visit from baseline to follow-up. They will be asked the question "*On a scale of 0 (No Itching) to 10 (Itching as bad as you can imagine), please rate the WORST itching that you felt over the last 24 hours*."

To determine the duration of itching, subjects will be asked "*Over the last 24 hours approximately how many hours, if any, did you itch?*". To determine the level of sleep disturbance due to itching, subjects will be asked "*On a scale of 0 (No sleep disturbance) to 10 (Awake all night), please rate how much your sleep was disturbed by itch last night*".

Subjects will be asked to rate their itch over the last 24 hours using a verbal rating score (VRS). This is a list of adjectives describing different levels of symptom intensity - no itch, mild, moderate and severe.

The secondary endpoints for Cohort 3 associated with NRS are:

- Change from baseline in the NRS for pruritus (worst itch) at Week 2
- Average change from baseline in NRS for pruritus (worst itch) over Days 8, 10 and 15
- Change from baseline in the NRS for sleep disturbance at Week 2
- Change from baseline in total duration of itching at Week 2
- Change from baseline in the VRS for pruritus at Week 2.

Patient Global Impression of Change (PGIC)

At the end of treatment (Day 15 or Early Termination Visit) subjects in Cohort 3 will be asked to rate their degree of improvement (or worsening) of their AD compared to before the start of treatment with study drug, using a 7-point scale. The scale ranges from 1 (very much approved) to 7 (very much worse).

The PGIC will be dichotomized into responders, defined as responses of 'Very Much Improved', 'Much Improved' or 'Minimally improved' (1, 2 or 3 on the scale above) and non-responders (4, 5, 6, or 7 on the scale above, plus missing data).

Body Surface Area (BSA)
Assessment of the percentage of a subject's BSA affected by AD will be made by best estimates of the Investigator at each visit for subjects in Cohorts 2 and 3. Affected BSA must be ≥ 10% and ≤40% at screening and must be ≥ 10% and ≤50% on Day 1 for the patient to be randomised.

The endpoints associated with BSA for Cohort 3 are change from baseline and percentage change from baseline at Week 2.

4.3. EXPLORATORY ENDPOINT

Ziarco Ointment Questionnaire
This is assessed at the end of the treatment phase for each cohort. Subjects will be asked a series of questions about their impressions of the study ointment they have used. Information regarding the ointment will be used to learn the practicalities of handling the ointment in a clinical setting for subsequent cohorts and clinical development (refer to Protocol Appendix 13 – Ziarco Ointment Questionnaire for a full list of questions).

4.4. SAFETY ENDPOINTS

The safety endpoints assessed for all 3 cohorts are:

- Adverse events
- Vital signs (blood pressure, pulse rate, and temperature) –change from baseline at each visit, maximum and minimum on-treatment measurement
- 12-lead Electrocardiograms (ECG) - change from baseline at each visit and maximum on-treatment measurement
- Laboratory safety tests (chemistry, haematology, and urinalysis) – change from baseline and percentage change from baseline

Modified Draize Score
For Cohort 1 subjects only, local toleration will be assessed by the modified Draize score prior to application of study ointment and until discharge from the CRU. For each assessment the grading value for erythema and eschar formation, oedema formation and desquamation will be recorded and the total of the three gradings will also be recorded. Grading is on a 5-point scale from 0-4, where 0=none to 4=severe.

4.5. PHARMACOKINETIC ENDPOINTS

Plasma ZPL-5212372 concentrations will be determined for all 3 cohorts. All concentration values will be reviewed prior to analysis and values that appear to be unexpectedly high due to potential contamination will be excluded and the reason(s) documented.

The safety review meeting for Cohort 1 data showed insufficient data to enable pharmacokinetic (PK) parameters to be calculated for Cohort 1, due to the very low and sporadic systemic exposure in a small number of subjects who had study ointment applied over 40% BSA.

PK parameters will be derived for Cohort 2 for Days 1 and 7. The ZPL-5212372 pharmacokinetic parameters AUC_{τ}, AUC_{last} and $t_{½}$ will be generated using non-compartmental methods. C_{max} and T_{max} will be determined directly from the data. The parameters are:

Day 1:

AUC_{τ} The area under the serum concentration versus time curve, from time 0 to 12 hours, as calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

C_{max} Maximum observed drug concentration.

T_{max} Time of the maximum serum concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.

Day 7:

AUC_{τ} The area under the serum concentration versus time curve, from time 0 to 12 hours, as calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

AUC_{last} The area under the serum concentration versus time curve, from time 0 to last available time point (48 hours), as calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

C_{max} Maximum observed drug concentration.

T_{max} Time of the maximum serum concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.

K_{el} Where possible, the apparent terminal elimination phase rate constant (k_{el}) will be calculated by linear regression of the log-linear plasma concentration-time curve. Only those time points judged to describe the terminal log-linear decline will be used in the regression. Values for this parameter will only be reported for an individual if a minimum of 3 measurable concentration-time-points during the log-linear portion of the terminal elimination phase, excluding Cmax, are available

$t_{½}$ Apparent first-order terminal elimination half-life will be calculated as $\ln 2/k_{el}$

$RAUC_{\tau}$ Accumulation ratio calculated as Day 7 AUC_{τ} / Day 1 AUC_{τ}

RC_{max} Accumulation ratio calculated as Day 7 C_{max} / Day 1 C_{max}

5. ANALYSIS SETS

5.1. SCREENED POPULATION

The screened population will include all subjects who signed the informed consent form and are screened for participation in this study. This population will only be used for the purposes of describing the subject disposition.

5.2. RANDOMISED SET

The randomised set will include all randomised subjects. This population will only be used for the purposes of describing the subject disposition.

5.3. FULL ANALYSIS SET (FAS)

The FAS will include all randomised subjects who receive at least one application of investigational medical product (IMP). Subjects will be included in their randomised treatment group even if they receive the wrong IMP. This population will be used for the primary efficacy analysis and most other analyses for efficacy and exploratory endpoints.

5.4. PER PROTOCOL (PP) ANALYSIS SET

The PP analysis set is only applicable for Cohort 3. It will include all subjects in the FAS who have not violated any inclusion or exclusion criteria and/or deviated from the protocol, in a way that could influence their efficacy assessment. For example subjects will be excluded if they:

- have poor IMP compliance, for example deviated from BID application over the 14 days and/or jar returned without being used. The IMP compliance will be assessed by a clinical review of dosing data and protocol deviations
- receive the incorrect IMP

Subjects will be included in their 'as treated' treatment group. Note that this will be the same as the randomised treatment because receiving the wrong IMP is a major deviation.

Data listings, including protocol deviations (Section 5.6), will be provided to identify subjects to be excluded from the PP analysis set. Precise reasons for excluding subjects will be documented prior to locking the database.

5.5. SAFETY ANALYSIS SET

The safety analysis set will include all subjects who receive at least 1 application of IMP. The safety analysis set summaries will be based on the actual treatment received for the whole duration of the study. The rules for handling data from subjects who receive study medication from the incorrect jar during the study will be decided on a case by case basis before database

lock. This analysis set will be used for all safety analyses.

5.6. PHARMACOKINETIC (PK) ANALYSIS SET

The PK analysis set will include all subjects in the FAS who received ZPL-521 with any valid post-baseline ZPL-521 plasma concentration result, including values below the lower limit of quantification (LLOQ). The PK analysis set summaries will be based on the actual treatment received for the whole duration of the study. The rules for handling data from subjects who receive study medication from the incorrect jar during the study will be decided on a case by case basis before database lock.

5.7. PROTOCOL DEVIATIONS

All protocol deviations will be reviewed and documented before database lock. Protocol deviations will be recorded by the site staff, study monitors and medical monitor reviewers. They may also be identified through programmable checks of the data.

Key protocol deviations include:

- Violations of inclusion and exclusion criteria. This includes unknown violations at enrolment and on-study violations, like taking a prohibited medication
- Poor IMP compliance
- Subject receiving the incorrect IMP

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All statistical tests for Cohort 3 will be 1-sided at the 0.05 level of significance and accompanied by a 2-sided 90% CI. There will not be any adjustments for multiple comparisons. No statistical testing will be performed with the data from Cohorts 1 and 2.

All summaries and listings will be presented by treatment group and by cohort. For Cohorts 1 and 2, adverse events and pharmacokinetic data will be presented by treatment group and BSA treated (10%, 40% and overall) to assess whether BSA impacts this data.

Only on-treatment records will be summarised for post-baseline visits, except follow-up, unless stated otherwise. A record is considered on-treatment if it is on or before the date of last study medication plus 1 day.

Continuous variables will be summarised using the number of observations (n), mean, standard deviation (SD), 95% Confidence interval (CI) of mean, median, minimum, and maximum. Geometric mean and coefficient of variation (CV) will be included for PK parameters, where appropriate. Categorical variables will be summarised using frequencies and percentages. The number of missing values will be presented in summary tables. The missing count will not include

subjects who have discontinued at earlier visits.

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more decimal place than the original values, and standard deviations should be printed out to 2 more decimal places than the original values. The minimum and maximum should report the same number of decimal places as the original values. The coefficient of variation will always be reported as a percentage to 1 decimal place. Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer.

Unless stated otherwise, baseline will be defined as the last non-missing measurement prior to administration of the first dose of IMP.

In by-visit summary tables the baseline will be summarised using all available data, but also for each visit using only the baseline data from subjects with available data at the visit; hence the mean change from baseline will equal the mean visit value – mean baseline value.

All data will be listed. Data listings will present study days in addition to dates, where study day is derived as (assessment date – first day of dosing + 1). The first day of dosing will be identified as Study Day 1.

All statistical analyses will be performed using SAS® (Version 9.2 or higher, SAS Institute Inc., Cary, NC, USA).

6.2. MISSING DATA

All possible efforts will be made to ensure that subjects complete all the required assessments. As missing data may potentially bias the outcome of the statistical analyses and the subsequent estimation of the magnitude of the treatment effect, different strategies will be applied to provide a balanced assessment of treatment efficacy.

Raw data will be reported in subject listings, but where imputed data are also presented (e.g. study start and stop days) they will be identified as imputed values in the listings.

Specific approaches for handling missing data are described below. Other missing data will not be imputed.

6.2.1. Efficacy Data

Missing efficacy data for Cohort 3 may result from:

- subject discontinuing from the study
- for data collected at the site the assessment may have been missed

For the sensitivity analysis of the primary efficacy endpoint missing values will be imputed using Markov Chain Monte Carlo (MCMC) multiple imputation methods. Means and variances from the

available data will be used to determine the MCMC starting values; imputed values will be selected with maximum likelihood methods. Initially, 200 MCMC runs will be generated before selecting the first imputed data set. An additional 24 data sets will be generated, separated by 100 iterations of the MCMC. The number of data sets may be increased if the analyses are not found to be sufficiently stable with respect to standard errors and p-values. Randomisation seed numbers will be specified for the MCMC run to ensure consistency and repeatability. These imputations will be performed separately within each treatment group.

The MCMC imputation assumes that data are missing at random.

To assess the influence of missing data several sensitivity analyses will be conducted for the primary efficacy endpoint, including a last observation carried forward (LOCF) analysis and worst case imputations when the missingness is considered informative; e.g. subject withdrew due to lack of efficacy. Details regarding which approaches will be used are in Section 8.1.1.

Missing categorical data will generally be considered as a non-response when dichotomizing responses for logistic modelling. Specific details are described in Section 8.

6.2.2. Pharmacokinetic Data

Concentrations of ZPL-5212372 reported as <LOQ will be taken as zero in the calculation of descriptive statistics. The data will be presented as <LOQ in the listing, with LOQ replaced by the relevant LOQ value.

For the calculation of PK parameters the following rules will apply:

- the value will be taken as zero for all values <LOQ before the first quantifiable concentration
- the value will be taken as missing for all values <LOQ after the last quantifiable concentration
- for values between quantifiable concentrations the pharmacokineticist will decide whether the value should be considered as missing or taken as zero base on the plausibility of a <LOQ value in the context of the whole concentration time profile. The pharmacokineticist will document this decision along with the justification.

Missing AUC and C_{max} values due to all concentrations recorded as <LOQ will be set to zero for the calculation of descriptive statistics, except for geometric mean where values will be treated equal to LOQ.

6.2.3. Safety Data

AEs with missing classification will be assumed to be the following:

- missing causality will be taken as treatment related

- missing seriousness will be taken as serious
- missing severity will be taken as severe

Handling of missing dates is detailed in the relevant sections below.

6.3. VISIT WINDOWS

There is no requirement for visit windows for Cohorts 1 and 2 as subjects will remain in the CRU for the duration of the study, so all assessments will be presented and analysed according to the visit assessment recorded.

For Cohort 3, all assessments will be presented and analysed according to the visit assessment recorded. Due to the short study duration visit windows will not be used. If possible, any early termination visits will be assigned to the closest study visit if they are on-treatment. Prior to database lock the data will be reviewed to identify any outlying visits and make decisions on how to deal with any issues. All decisions will be documented prior to database lock.

6.4. STRATIFICATION

No stratification is used for the randomisation in Cohorts 1 and 2.

The randomisation for Cohort 3 is stratified by baseline EASI (≤20 or >20). This will be checked and any subjects who were misallocated to the wrong strata will be summarised according to the group they should have been assigned to. Misallocations will be listed.

6.5. SUBGROUPS

The following subgroups will be considered for Cohort 3 only:

- Stratification subgroup: baseline EASI (≤20 or >20)

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. PATIENT DISPOSITION AND WITHDRAWALS

The following will be tabulated over all screened subjects (the number of subjects in the screened set will be used as the denominator in the calculation of percentages):

- Number of subjects screened
- Number (%) of subjects who enter the washout period
- Number (%) of subjects who withdraw prior to the washout period
- Number (%) of subjects who withdraw prior to randomisation
- Number (%) subjects withdrawing before randomisation by reason

- Number (%) of subjects randomised

The following will be tabulated for each treatment group (the number of subjects in the Randomised set will be used as the denominator in the calculation of percentages):

- Number of subjects randomised
- Number (%) of subjects who complete the treatment period
- Number (%) of subjects who withdraw during the treatment period
- Number (%) subjects withdrawing during treatment period by reason
- Number (%) of subjects who complete the post-dose study follow-up
- Number (%) of subjects who withdraw between last dose of study medication and the post-dose follow-up visit.
- Number (%) subjects who withdraw during follow-up by reason

In addition the number (%) of subjects in each analysis set will also be tabulated.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demography (gender, race, ethnicity, age [years], weight [kg], height [cm] and BMI [kg/m^2]) will be summarised overall and by treatment group for the FAS. Age, weight, height and BMI will be summarised using summary statistics for continuous variables. Gender, race, ethnicity and Fitzpatrick Skin Type Classification will be summarised using summary statistics for categorical variables.

Age = (Day 1 date - date of birth + 1)/365.25 truncated to complete years.

For Cohorts 2 and 3, the following baseline characteristics will be summarised using descriptive statistics by treatment group and overall, for subjects in the FAS; except for EASI (categorical), VRS and IGA which will present counts and percentages:

- Duration of atopic dermatitis (years)
- EASI
- EASI (categorical): ≤20 and >20
- % BSA Affected
- IGA score
- NRS for worst pruritus (over 24 hours)*
- duration of itching (over 24 hours)*
- NRS for sleep disturbance*
- VRS for pruritus (over 24 hours)*

* Only summarised for Cohort 3.

Duration of atopic dermatitis in years will be calculated from the date of onset recorded on medical history relative to Day 1 i.e. Day 1 date - onset date divided by 365.25.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) Version available. Summaries will be presented for the FAS by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages for each treatment group and overall. Each subject will be counted only once in each SOC or SOC/PT summary.

7.4. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using the latest WHO Drug Dictionary version available. Medication will be presented for the safety population by ATC level 2 (therapeutic main group) and ATC level 5 (standardized medication name) with counts and percentages for each treatment group and overall. A subject who took more than one medication will be counted only once if these medications belong to the same extended ATC classification.

In addition, a summary of prior emollients (excluding study emollients) and concomitant emollients will be presented for Cohorts 2 and 3 with counts and percentages for each treatment group. Prior emollients will exclude study emollients which will be identified as emollients started prior to dosing but on or after the screening visit. The study emollients used were [redacted] for Cohort 2 and [redacted] or Epaderm for Cohort 3. A clinical review of all unique medications will be done prior to database lock to identify emollients.

Prior medications will be defined as those medications started prior to the administration of study drug on Day 1. Concomitant medications will be defined as those medications taken following the first administration of study drug on Day 1. Hence medications started before study dosing, but continuing after are considered as both prior and concomitant medications. The listing of medications will identify prior and concomitant medications.

If either the start or stop date of medication is missing, the worst or most conservative case will be considered when assigning medications to categories. So for a missing start date (where stop date is after date of first dose) the date will be imputed as the date of first dose; for a missing stop date the date will be imputed as the subject's last study day or start date if start date is after last dose. If a partial date is recorded, the following convention will be used to assign the medication:

- If a partial date is missing a start day and the month/year is the same as first dose date then use first dose date, else '01' will be used for the day; if a start date is missing a month and the year is the same as first dose date then use first dose date, else January will be used for the start month.
- If a partial date is missing a stop day and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing a month and the year is the same as last study date then use last study date, else December will be used for the stop month.

8. EFFICACY

As Cohort 1 includes healthy volunteers no efficacy data will be collected. Though some efficacy assessments are included for Cohort 2 the data will only be listed and no formal comparisons will be made between the treatment groups. Consequently efficacy will only be assessed for Cohort 3. Hence the following analyses apply to Cohort 3 data.

The observed data summaries for all efficacy endpoints, except PGIC, will only use 'on-treatment' records (i.e. on or before the date of last study medication plus 1 day) for all visits, except baseline and follow-up.

For all ANCOVA analyses the treatment least square means (LS means) and LS mean standard errors, treatment difference estimate, standard error, 1-sided p-value, and 90% CI will be presented. The corresponding SAS ANCOVA output will also be outputted for internal statistical review.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary endpoint is the percentage change from baseline to Week 2 in the EASI score. Baseline will be taken as the last non-missing measurement prior to administration of the first dose of IMP, this should be Day 1 for the primary endpoint.

The observed percentage change from baseline to Week 2 in the EASI score will be analysed for the FAS with an Analysis of Covariance (ANCOVA) model that includes baseline score as a covariate and treatment (ZPL521 or placebo). The treatment effect will be estimated with the difference between the least square means (LS means), defined as ZPL521 - placebo.

The ANCOVA analysis assumptions will be checked by evaluating the model residuals. A Shapiro-Wilks test will be performed on the residuals; a p-value > 0.1 will be considered proof of normality. If the Shapiro-Wilks p-value is ≤ 0.1, the residual plot will be evaluated for symmetry. If the evaluation of residuals indicates a problem with the model assumptions, a transformation of the data will be considered, including a rank-transformation of the data.

The EASI score will be summarised by treatment and visit for the FAS with observed data. Summaries will present the descriptive statistics for baseline, change from baseline and percentage change from baseline data.

Patient profile plots by treatment group, of the percentage change from baseline in EASI score will also be presented. Note that only observed data will be included in these plots; i.e. no imputations will be used.

8.1.1. Sensitivity Analyses of the Primary Endpoint

The robustness of the primary analysis will be evaluated by repeating the primary analysis with

the per-protocol analysis set.

In addition, the following sensitivity analyses will be conducted using the FAS:

- an analysis where missing values will be imputed using MCMC multiple imputation methods (see Section 6.2.1). These imputations will be performed separately within each treatment group.
- an analysis using a worst case imputation for missing data considered as 'informative'. Missing data will be reviewed by the study team to identify situations where the missingness is considered informative; e.g. subject withdrew for lack of efficacy. In these situations the Week 2 score will be taken as equal to the worst score recorded for either treatment group. For the 'non-informative' values the MCMC imputed values will be used. Note, the worst case imputation i.e. worst score, will occur after the MCMC values have been generated.
- an analysis using an LOCF method for handling missing data

In addition, the EASI score will be summarised by treatment and visit for the FAS with MCMC imputation data. For this summary, the mean of the imputed data for a subject is used in the calculation. Hence when multiple imputations are performed for the analysis, a missing data point will be estimated with the mean of the multiple different imputations; this individual mean will be used to calculate the overall treatment summary statistics.

8.1.2. Additional Analyses of the Primary Endpoint

The percentage change from baseline to Day 5, Day 8 (Week 1) and Day 10 will also be analysed for the FAS using the same approach as for the primary analysis.

Additional summaries and analyses of the Week 2 data will be performed for the subgroups detailed in Section 6.5. These analyses will be based on the FAS and will be the same as the primary analysis.

8.2. SECONDARY ENDPOINTS AND ANALYSIS

8.2.1. EASI-50 and EASI-75

The proportion of subjects who achieve an EASI-50 response will be summarised in the FAS with counts and percentages by treatment group at each visit. The number of missing values will also be presented.

An exact logistic regression analysis will be performed at Week 2. The model will include treatment and baseline EASI score. The odds ratio, p-value and associated exact 90% CI will be presented. Subjects with missing responses will be counted as non-responders.

The proportion of subjects who achieve an EASI-75 response will be analysed in the same way as described for the EASI-50.

The cumulative proportion of subjects achieving a ≥x% reduction in EASI at Week 2 will be plotted against x, with different lines for each treatment group. Subjects with missing data will be regarded as having the worst change from baseline and labelled as such on the plot. Horizontal reference lines will be drawn that relate to the 0, 25, 50 and 75% reductions in EASI scores.

8.2.2. EASI Components

The 4 EASI component scores (erythema, oedema/papulation, excoriation and lichenification) will be summarised by treatment and visit for the FAS. Summaries will present the descriptive statistics for baseline, change from baseline and percentage change from baseline data.

Percent change from baseline to Week 2 for each EASI component will be analysed for the FAS with an ANCOVA model. The model will include baseline value and treatment. The treatment effect will be estimated with the difference between least square means (LS means), defined as ZPL521 - placebo. The estimate, standard error, 1-sided p-value, and 90% CI will be presented.

The analysis will be repeated for all other time points (Day 5, Day 8 [Week 1] and Day 10).

8.2.3. Investigators Global Assessment (IGA)

IGA will be summarised for the FAS with counts and percentages by treatment at each visit. The number of missing values will also be presented. Shift tables of change from baseline will also be presented with marginal totals.

IGA response will be summarised at each visit with counts and percentages; missing responses will also be tabulated. An exact logistic regression analysis will be performed for Week 2. Baseline IGA, stratification variable (baseline EASI; ≤20 or >20) and treatment will be included in the models as factors; subjects with missing responses will be counted as non-responders. The odds ratio, p-value and associated exact 90% CI will be presented. This analysis will be repeated for IGA success.

8.2.4. Numerical Rating Scale (NRS)

NRS for pruritus will be summarised by treatment and visit for the FAS. Summaries will present the descriptive statistics for baseline, change from baseline and percentage change from baseline data.

Change from baseline to Week 2 of the NRS for pruritus will be analysed for the FAS with an ANCOVA model. The model will include baseline NRS, stratification variable (baseline EASI; ≤20 or >20) and treatment. The treatment effect will be estimated with the difference between least square means (LS means), defined as ZPL521 - placebo. The estimate, standard error, 1-sided p-value, and 90% CI will be presented.

This analysis will be repeated for the average change from baseline in NRS pruritus over Days 8, 10 and 15.

Summaries over time will be presented for the FAS for the following NRS endpoints:

- NRS for sleep disturbance
- total duration of itching

All pruritus data will be listed.

8.2.5. Verbal Rating Score (VRS)

The VRS will be summarised for the FAS with counts and percentages by treatment at each visit. Shift tables of change from baseline will also be presented with marginal totals.

8.2.6. Patient Global Impression of Change (PGIC)

The PGIC scores will be summarised for the FAS with counts and percentages in each treatment group. All data collected will be included.

The PGIC will also be dichotomized into responders, defined as responses of 'Very Much Improved', 'Much Improved' or 'Minimally improved' (1, 2 or 3) and non-responders (4, 5, 6, or 7 plus missing data). The PGIC responder variable will be analysed in the FAS with exact logistic regression. The stratification variable (Baseline EASI; ≤20 or >20) and treatment will be included in the model as factors; the odds ratio, p-value and associated exact 90% CI will be presented.

8.2.7. Body Surface Area (BSA)

The percentage BSA affected will be summarised at each visit, including change and percentage change from baseline, by treatment group, using the FAS.

Change from baseline to Week 2 in the BSA will be analysed for the FAS with an ANCOVA model that includes baseline score, stratification variable (baseline EASI; ≤20 or >20) and treatment. The treatment effect will be estimated with the difference between the least square means (LS means), defined as ZPL521 - placebo. The estimate, standard error, 1-sided p-value, and 90% CI will be presented.

8.3. EXPLORATORY ENDPOINT

8.3.1. Ziarco Ointment Questionnaire

The categorical responses to the Ziarco ointment questionnaire will be summarised by treatment for each of the cohorts using the FAS. All data collected will be included.

All data will be listed.

9. ANALYSIS OF PHARMACOKINETICS

9.1. CONCENTRATION DATA

Cohorts 2 and 3 concentration data will be summarised for the PK analysis set at each visit and time point using descriptive statistics (n, median, minimum, maximum, missing and frequency of values <LOQ). The summary for Cohort 2 will be by treatment group and BSA treated and for

Cohort 3 by treatment group. For samples after the start of dosing only concentrations collected within a 15% window of the protocol specified time point will be included. Concentration values reviewed prior to the PK analysis and found to be unexpectedly high due to potential contamination will also be excluded. Values below the LLOQ will be taken as 0 for summaries.

An individual subject profile plot will be presented for the trough concentration data for Cohort 3 on the linear scale. The BSA treated will be presented along with the Subject ID. The actual sampling time will be used on the x-axis. Values below the LLOQ will be taken as 0 for linear plots.

All plasma concentration data will be listed for all cohorts. The listing will include BSA treated, actual sampling times and deviations from nominal sampling times. Values below the LLOQ will be listed as <LOQ (with relevant value for LOQ) in listings.

9.2. PHARMACOKINETIC PARAMETER DATA

There is insufficient data to enable PK parameters to be calculated for Cohort 1 due to the very low and sporadic systemic exposure in a small number of subjects who had study ointment applied over 40% BSA.

The PK parameters for Cohort 2 will be summarised by BSA treated and Day for the PK analysis set. Geometric mean and CV will be presented for all parameters except $t_{½}$. Due to the low sporadic exposure T_{max} will not be summarized.

All PK parameters for Cohort 2 will be listed.

10. SAFETY

10.1. DRAIZE SCORE

The modified Draize score which assesses local toleration will be listed. This is only collected for Cohort 1.

10.2. EXTENT OF EXPOSURE

For Cohorts 1 and 2, the number of days on treatment, the average daily volume administered and average daily amount of ointment used (based on a density of 1.1089 g/mL) will be summarised using descriptive statistics by treatment group for the FAS. The average daily volume administered and average daily amount of ointment used will be split by BSA treated within a cohort.

- Days on treatment = date of last dose – date of first dose +1
- Daily volume administered = Total volume administered / number of days on treatment
- Daily amount of ointment used = daily volume administered * density

For Cohort 3 the number of days on treatment and daily amount of ointment used will be summarised using descriptive statistics by treatment group for the FAS.

- Daily amount of ointment used = (total weight of dispensed jars – total weight of returned jars) / days on treatment

If a jar is not returned then it will be assumed that the weight for this jar is missing and no daily amount of ointment used will be calculated for the subject.

Study drug administration, including all the variables specified above, will be listed.

10.3. ADVERSE EVENTS

AEs will be coded using the latest MedDRA version available.

AEs will be considered treatment-emergent (TEAE) unless there is clear indication that the event occurred prior to first dose of study drug. AEs present prior to the first dose of study drug administration that increased in severity or relationship to study drug after the first dose of study drug will be classed as TEAE. Events with missing or partial dates will be handled such that in the absence of contradictory information an AE is treatment emergent. So for a missing start date (where stop date is after date of first dose or missing) the date will be imputed as the date of first dose; for a missing stop date the date will be imputed as the date of the subject's last study day. If a partial date is recorded, the following convention will be used to assign the AE:

- If a start date is missing the day information and month/year is the same as first dose date then use first dose date, else '01' will be used for the day; if a start date is missing the month and the year is the same as first dose date then use first dose date, else January will be used for the start month; if start date is missing (i.e. even the year is unknown) then the AE will be considered not treatment emergent and the date will be set to the date of informed consent.
- If a stop date is missing the day information and month/year is same as the subject's last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing the month and year is the same as last study date then use last study date, else December will be used for the stop month.

All AEs will be listed however only TEAEs will be included in the summary tables. An overall summary will present the number and percentage of subjects by treatment group and BSA treated for Cohorts 1 and 2 and by treatment group for Cohort 3. The summary will include:

- any TEAE
- any TEAE considered as related to study drug (evaluated by the investigator as Related, Possibly Related or Probably Related or not reported)
- any serious TEAE
- Maximum intensity TEAE of none, mild, moderate, severe ; i.e. a subject with TEAEs at

different intensities will be summarised at the most severe intensity

- any TEAE leading to study drug discontinuation
- any TEAE leading to death

The table will also include the total number of TEAEs reported in each treatment group. The total number of unique terms within subjects will also be presented, counting each TEAE only once within each subject.

The number and percentage of subjects with TEAEs will be presented by SOC, PT and treatment group and BSA treated for Cohorts 1 and 2 and by SOC, PT and treatment group for Cohort 3. Subjects with multiple TEAEs within a SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination. Similar summaries will be presented for related TEAEs.

Summaries of TEAEs by maximum intensity (Mild, Moderate, or Severe) will be presented for TEAEs.

All TEAEs will be listed by subject and start date. Separate listings of serious TEAEs and TEAEs leading to discontinuation of study drug will also be generated.

10.4. LABORATORY EVALUATIONS

The change from baseline and percentage change from baseline in haematology, chemistry, and continuous urinalysis parameters will be summarised by treatment group using descriptive statistics. Discrete urinalysis parameters will be summarised with counts and percentages by treatment group. The number of normal and abnormal (low and high) records will also be summarised with counts and percentages by treatment group. Baseline and all protocol specified on treatment (i.e. on or before the date of last study medication plus 1) visit data will be summarised. If a baseline value is missing for a parameter, the screening value will be used as the baseline value.

Subjects who satisfy the criteria for values of potential clinical concern will be summarised and listed separately. The summary will present the number of subjects with at least one on-treatment visit value (including unscheduled visits) satisfying the criteria. The listing will include all data for the subject and parameter which satisfied the criteria. The record satisfying the criteria will be identified on the listing. The criteria are:

Table 2: Criteria for Laboratory Safety Values of Potential Clinical Concern

Category	Parameter	Criteria
Haematology	Haemoglobin	<0.8 x baseline
	Haematocrit	<0.8 x baseline
	WBC	<2.5 or >17.5 x $10^3/mm^3$
	Platelets	<75 or >700 x $10^3/mm^3$
Chemistry	GGT	>3 x ULN
	Creatinine	>1.3 x ULN
	Urea	>1.3 x ULN
	Glucose, fasting	<0.6 x LLN or >1.5 x ULN
	Uric acid	>1.2 x ULN
	Sodium	<0.95 x LLN or >1.05 x ULN
	Potassium	<0.9 x LLN or >1.1 x ULN
	Calcium	<0.9 x LLN or >1.1 x ULN
	Albumin	<0.8 x LLN or >1.2 x ULN
	Total protein	<0.8 x LLN or >1.2 x ULN
Urinalysis	Urine WBC	≥6/HPF
	Urine RBC	≥6/HPF

LLN=lower Limit of Normal; ULN=Upper Limit of Normal.

Liver function tests (ALT, AST, alkaline phosphatase and total bilirubin) will also be summarised. The number of subjects with any on treatment visit (including unscheduled visits) value either >1.5 x ULN or >2 x ULN or >3 x ULN will be summarised for each liver function test parameter.

All laboratory data will be listed; change from baseline, percentage change from baseline and abnormal alerts will be included in the listings. Screening laboratory tests for serology, drug screen and breath alcohol test will be listed, but not summarised.

10.5. VITAL SIGNS

Systolic blood pressure (BP), diastolic BP and pulse will be summarised by visit, time point and treatment group using descriptive statistics for the observed and change from baseline values. Systolic BP, diastolic BP and pulse will be collected in duplicate at each time point. The mean of these 2 measurements will be derived prior to summarizing the data. If a baseline value is missing for a parameter, the screening value will be used as the baseline value. All vital sign data, including the mean values that are summarised, will be listed.

The maximum and minimum values will be derived for each subject over all on-treatment visits (i.e. on or before the date of last study medication plus 1) from all scheduled and unscheduled individual readings and the number (%) of subjects in each of the following categories will be tabulated:

Table 3: Criteria for Vital Signs

Parameter	Category	Criteria
Systolic BP	1	< 90 mmHg*
		≥ 90 mmHg
	2	< 30 mmHg change from baseline
		≥ 30 mmHg change from baseline*
Diastolic BP	1	< 50 mmHg*
		≥ 50 mmHg
	2	< 20 mmHg change from baseline
		≥ 20 mmHg change from baseline*
Pulse	1	< 40 bpm*
		≥ 40 – ≤120 bpm
		> 120 bpm*
	2	< 40 bpm and at least one value > 120 bpm
		< 40 bpm and no value > 120 bpm
		≥ 40 bpm

* Indicates criteria to be identified in listing.

Vital signs data will be listed. The listing will include actual sampling times and deviations from nominal sampling times. The listing will flag records that satisfy the above criteria.

10.6. ECG

The mean of the triplicate measurements will be derived prior to summarizing the data. If a baseline value is missing for a parameter, the screening value will be used as the baseline value.

ECG parameters, and their change from baseline, will be summarised at each time point using descriptive statistics.

For Cohorts 1 and 2, subjects who satisfy the criteria for values of potential clinical concern will be summarised and listed separately. The summary will present the number of subjects with at least one on-treatment (i.e. on or before the date of last study medication plus 1) visit value (including unscheduled visits) satisfying the criteria. The listing will include all data for the subject which satisfies the criteria. The record satisfying the criteria will be identified on the listing. The criteria are:

Table 4: Criteria for ECG Safety Values of Potential Clinical Concern

Parameter	Category	Criteria
QT/QTcF	1	< 500 msec
		≥ 500 msec*
	2	Increase from baseline < 30 msec
		Increase from baseline ≥ 30 msec and <60 msec*
		Increase from baseline ≥ 60 msec*
PR	1	< 300 msec
		≥ 300 msec*
	2	< 25% increase from baseline
		≥ 25% and < 50% increase from baseline when baseline > 200msec*
		≥ 25% and < 50% increase from baseline when baseline ≤ 200msec
		≥ 50% increase from baseline when baseline > 200msec*
		≥ 50% increase from baseline when baseline ≤ 200msec*
QRS	1	< 200 msec
		≥ 200 msec*
	2	< 25% increase from baseline
		≥ 25% and < 50% increase from baseline when baseline > 100msec*
		≥ 25% and < 50% increase from baseline when baseline ≤ 100msec
		≥ 50% increase from baseline when baseline > 100msec*
		≥ 50% increase from baseline when baseline ≤ 100msec*

* Indicates criteria to be identified in listing.

All ECG data will be listed, including the mean values that are summarised.

10.7. PHYSICAL EXAMINATION

A full physical examination will be performed at screening; post-screening physical exams will only include selected body systems (as a minimum, general appearance, heart, lungs and skin), determined by clinical findings and any AEs reported. All physical exam data will be listed.

11. INTERIM ANALYSES

Progression from Cohort 1 to Cohort 3 will be dependent on the demonstration of adequate safety within the protocol defined boundaries. There will be a safety review meeting between each cohort to assess safety and PK. The safety review will be conducted on blinded data, however some members of the Safety Review Team may be unblinded to treatment. The Safety Review Team will decide whether to proceed to the next cohort. In the event that it is decided not to proceed to the next cohort, the reviewers may decide to modify the study within the

boundaries of the adaptive features and continue, to submit a substantial protocol amendment or suspend the study.

Further details on the operation of the safety review meetings will be defined in a separate document.

12. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The changes from the analyses specified in the protocol are:

1. The definition of responders for IGA score in the protocol has been further clarified and made consistent with the sponsor's previous atopic dermatitis study. The definition has changed from reduction from baseline of at least 2 points, to those subjects who achieve a score of 'Clear' or 'Almost clear', or a reduction of ≥ 2 from baseline. An additional definition of IGA success has also be defined as those subjects who achieve a score of 'Clear' or 'Almost clear'.

2. The protocol stated that the changes from baseline at Week 2 in NRS sleep disturbance and duration of itch will be analysed using ANCOVA, however it has been decided that it is sufficient to only summarize these endpoints by treatment group and visit. Only the NRS endpoint daily pruritus will be analysed.

3. The protocol stated that the Draize score for Cohort 1 would be summarised by treatment group and the change from baseline in Draize score would also be summarised using categorical shift tables. However, the safety review of Cohort 1 showed that there were very few changes in Draize score; it was therefore decided that summaries were not necessary for this endpoint and the data would only be listed.

4. The PK analyses described in the protocol have been modified to reflect the very low and sporadic systemic exposure observed during the safety review meetings for Cohorts 1 and 2.

13. REFERENCE LIST

1. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ & Graeber M (2001). The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. . Exp Dermatol., Feb;10(1):11-8.

2. Draize JH, Woodard G & Calvery H (1944) Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 82: 377-390.

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The following tables are planned to be generated and numbering is indicative only and may be updated for final reporting based on CSR requirements.

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