NOVARTIS

Global Clinical Development - General Medicine

ZPL389

Clinical Trial Protocol CZPL389A2203 / NCT03517566

A randomized, double-blind, placebo-controlled multicenter dose-ranging study to assess the safety and efficacy of multiple oral ZPL389 doses in patients with moderate to severe atopic dermatitis (ZEST trial)

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List of abbreviations

γ-GT	Gamma-glutamyl transferase
ACR	albumin-creatinine ratio
AD	atopic dermatitis
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	Absolute Neutrophil Count
Anti-HBc	Anti-Hepatitis B core antigen antibody
Anti-HBs	Anti-Hepatitis B surface antigen antibody
AST	aspartate aminotransferase
AV	atrioventricular
BMI	Body Mass Index
BSA	Body Surface Area
BUN	blood urea nitrogen
[redacted]	[redacted]
CFR	Code of Federal Regulation
CI	confidence interval
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DILI	Drug induced Liver injury
[redacted]	[redacted]
DMC	Data Monitoring Committee
EASI	Eczema area and severity index
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medical Agency
EOT	End of Treatment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
H4R	Histamine-4 receptor

HBsAg	Hepatitis B surface Antigen
HIV	human immunodeficiency virus
[redacted]	[redacted]
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
i.v.	intravenous
LDH	Lactate Dehydrogenase
LFT	Liver function test
[redacted]	[redacted]
MCPMod	Multiple Comparison Procedures – Modelling
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
MI	Multiple imputation
mL	milliliter(s)
MMRM	Mixed effect Model Repeat Measurement
[redacted]	[redacted]
NOAEL	No observed adverse effect level
NRS	Numerical rating scale
o.d.	once daily
PCR	Protein creatinine ratio
PD	Pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PoC	Proof of Concept
PRO	Patient Reported Outcome
PSW	Premature Subject Withdrawal
PT	Prothrombin time
[redacted]	[redacted]
QTc(F)	Corrected QT interval (by Fredericia's formula)
RNA	Ribonucleic acid
SAE	Serious Adverse Event

[redacted]	[redacted]
sCR	serum Creatinine
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
TBL	Total Bilirubin
TCS	Topical Corticosteroids
TD	Treatment discontinuation
TdP	Torsades de Pointes
Th2	T-helper 2 cells
TSLP	Thymic stromal lymphopoietin
ULN	upper limit of normal
[redacted]	[redacted]
[redacted]	[redacted]
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of consent
WOCBP	Women of child bearing potential

Glossary of terms

Baseline	Day 1: subjects who are eligible will be randomized
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 30 mg once daily)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
IGA Response	IGA response is defined as achieving an IGA score of 0 (clear) or 1 (almost clear) and at least 2 points reduction from Baseline and no use of confounding therapy as adjudicated up to the assessment time point.
Medication pack number	A unique identifier on the label of each investigational drug package
Patient	A person with the condition of interest being studied
Period	Interval of time in the planned conduct of a study. A period is associated with a purpose (e.g. screening, treatment, follow-up), which applies across all arms of a study.
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Subject	A patient participating in this study
Subject number	A unique number assigned to each subject upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Amendment 3 (02 September 2019)

Amendment rationale

Per the original protocol, even though chronic toxicity studies showed no hepatotoxic effects, due to the fact there was at the time limited human data with ZPL389, subjects were not allowed to have any value of AST/ALT/ALP above the upper limit of normal in order to join this phase 2 study. With the recent results from phase 1 study in healthy volunteers (CZPL389A2101) that tested high exposures of ZPL389, no liver abnormalities were seen. Therefore, exclusion limit for AST/ALT/ALP have been increased to 1.5 ULN to allow patients with only minor elevations of AST/ALT/ALP into the study and to prevent unnecessary exclusion of subjects from the study participation. Subjects would still need to fulfill other criteria (e.g. absence of HBV, HCV, prior liver disease, hepatotoxic concomitant medication) in order to be eligible for the study, and will be closely monitored for LFT during the study, therefore safety of subjects would not be compromised.

A clarification about the use of H1 antihistamines has been added. Unless these have a potential for QT interval prolongation (prohibited for all subjects) or have a sedative effect [redacted], these are allowed if on a stable dose or used short term (e.g. to treat allergies).

Changes to the protocol

The sponsor has also used this opportunity to make operationally relevant or typographical modifications and/ or provide clarifications.

All changes made to the protocol are listed in the table below.

Section	Changes made
Section 3.5, Section 5.4 and Section 9.7	Addition of a potential interim analysis
Section 3.6	Updated with results of pivotal Embryo-fetal development toxicology studies and CZPL389A2101 study
Section 4	Number of study sites has been updated
Section 4.2	Clarification added to Exclusion criterion #2 on skin infection Exclusion criterion #10 has been modified to • include subjects with AST/ALT/ALP up to 1.5 upper limit of normal (ULN) • clarify abnormal values for Potassium and Magnesium • Allow one central lab retest for lab abnormalities outside the respective cut-off criteria during screening period Clarification added to Exclusion criterion #11 on basal cell carcinoma of the skin Clarification added on the form of hormonal contraception allowed in Exclusion criterion #15
Section 5.2.2 and Table 5-1	Removal of Vitamin E as prohibited component of moisturizers
Section 5.5.4	Clarification on the number of doses to be taken until week 16 visit

[redacted]	[redacted]
Section 5.5.6	Clarification added for use of an alternative TCS as rescue medication
Section 5.5.8, Table 5-1	For subjects who discontinued early, action taken on prohibited medication during follow up period has been modified Clarification on the use of H1 Antihistamines Information on use of ibuprofen or topical NSAID has been added
Section 6.2	Clarification added for collection of subject's baseline characteristics
Section 6.2.1	Clarification on the type of test done for Hep C
Section 6.5.5.1 and Table 14-2	PT/INR has been added to unscheduled visit
Section 6.5.6.1	Microscopy result entry in CRF has been removed as the result will be available in central laboratory data
Section 6.6.4	Clarification on the requirement of availability of CYP2D6 test results before randomization for subjects taking moderate CYP1A2 inhibitor and adherence to wash out period
[redacted]	[redacted]
Section 7.3	In case of a Liver event, requirement of completion of applicable questionnaire for adjudication has been added
Section 7.5	Any increase from Baseline of 30 msec in QTcF (Fridericia) interval for males and females has been added to the definition of a notable QTc value

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (11 September 2018)

Amendment rationale

The protocol is amended to incorporate changes following interim results from Phase I trial in healthy volunteers (CZPL389A2101). [redacted]

Based on the Phase I study results and potential drug-drug interaction risk, the protocol is amended to include a precautionary measure to minimize the risk of higher exposure to ZPL389 that may occur in subjects who are poor CYP2D6 metabolizers. This measure includes identifying subjects that are poor CYP2D6 metabolizers prior to study treatment start and prohibiting use of moderate inhibitors of CYP1A2 (including hormonal contraception), in these subjects (CYP2D6 metabolizers). As per previous protocol, strong CYP1A2 inhibitors are still prohibited for all subjects. Additionally Phase I study results have shown that more time is needed to achieve [redacted] than shown by previous studies, therefore the timing of the post dose ECG is changed from 0.5h to 2h. On days of site visits, subjects are asked to fast 3 hours before the visit, [redacted] ECG parameters may be impacted by the intake of food. However, due to no food effect seen on overall drug exposure in Phase I study, fasting before and after drug intake on non-visit days is no longer necessary.

[redacted]

Changes to the protocol

[redacted]

All changes made to the protocol are listed in the table below.

Section	Changes made
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Section 3.1, Figure 3-1 and Table 6-1	The screening period has been extended up to 4 weeks (to allow time to get the [redacted]), extending the total study duration from 23 to 24 weeks
Section 3.4, Section 4.1, Section 5.2.2 and Section 6	The use of bland emollient has been changed to once daily instead of twice
Section 3.3 and Section 3.6	Updated with relevant interim data from study CZPL389A2101
Section 3.4	Removal of the sentence referring to the extension study as this was misplaced

Section 4.2	Exclusion criteria #15 has been modified to prohibit hormonal contraception for poor CYP2D6 metabolizers (as hormonal contraception is moderate inhibitor of CYP1A2) Deletion of the text about additional exclusion applied by investigator
Section 4.3 and Section 4.4	[redacted]
Section 5.4	Clarification on when unblinding would occur
Section 5.5.4 and Section 6	Fasting requirement before and after taking study medication at home has been removed.
Section 5.5.6	Allowing hydrocortisone 2.5% ointment as rescue medication for sensitive areas
Section 5.5.8	Addition of moderate CYP1A2 inhibitors as prohibited concomitant medication for CYP2D6 poor metabolizers Clarification that eye drops are not considered systemic immunosuppressive treatment.
Section 5.6	Clarification on EOT, Withdrawal of consent and early study termination
Section 6	Clarification that subjects should be fasted 3 hours before site visits and until the last ECG is performed Visit days for Week 16 and Week 20 visits have been updated to 113 and 141 days respectively. Therefore dosing at site on Week 16 visit has been removed. A clarification has been added on when [redacted] sample will be collected at Week 16 visit Unplanned ECG has been added in the table of assessment and time of Post dose ECG at Baseline and Week 4 changed from 0.5h to 2 hours postdose [redacted]
Section 6.6.1 and Section 8.3	Allowing Patient Reported Outcomes (PROs) to be collected on paper should the electronic device not be working
[redacted]	[redacted]

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

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The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment

Amendment 1 (30 January 2018)

Rationale

The original protocol is amended to incorporate health authority feedback prior to the start of enrolment as listed in the table below.

Section	Changes made
[redacted]	[redacted]
Section 4.1	EASI score at Screening visit for inclusion into trial changed from 12 to 16
Section 4.2 and Section 7.5	Exclusion threshold and notable value for resting QTcF for female changed from ≥460 to ≥470 msec
Section 5.6 and Section 7.5	Discontinuation criteria for cardiac disorders aligned with CTCAE grade 2 events
Section 6	Time of Post dose ECG at Baseline and Week 4 changed to 30 mins postdose
[redacted]	[redacted]

The sponsor has used this opportunity to simplify and update sections regarding sample size and statistical analysis. Other minor corrections were made such as adding the requirement for fasting 1 hour before ECG measurements.

All changes from the original protocol v00 are indicated in red underlined text (insertions) or red strikethrough (deleted text) in the track changes version of this protocol amendment.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CZPL389A2203
Full Title	A randomized, double-blind, placebo-controlled multicenter dose ranging study to assess the safety and efficacy of multiple oral ZPL389 doses in patients with moderate to severe atopic dermatitis (ZEST Trial)
Brief title	A study to assess the safety and efficacy of ZPL389 doses in patients with moderate to severe atopic dermatitis
Sponsor and Clinical Phase	Novartis, Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine the dose-response relationship of ZPL389 for key efficacy and safety parameters in order to define the most appropriate dose(s) for further development of ZPL389 in subjects with moderate to severe atopic dermatitis.
Primary Objective(s)	To characterize the dose-response relationship of ZPL389 in subjects with moderate to severe atopic dermatitis assessed by Investigator's global assessment response at Week 16
Secondary Objectives	1. To characterize the dose-response relationship of ZPL389 in subjects with moderate to severe atopic dermatitis assessed using the percent change from Baseline in Eczema Area and Severity Index after 16 weeks of treatment 2. To evaluate the efficacy across different dose levels as assessed by Eczema Area and Severity Index and Investigator's global assessment compared to placebo over time 3. To assess the safety and tolerability of different doses of ZPL389 as compared to placebo
Study design	This is a randomized, double-blind, placebo-controlled, parallel-group study to assess safety and efficacy of ZPL389 in subjects with moderate to severe atopic dermatitis with a total study duration up to 24 weeks
Population	The study population will consist of female and male subjects aged 18 years or older with moderate or severe atopic dermatitis

Key Inclusion criteria	• Written informed consent
	• Chronic atopic dermatitis (according to American Academy of Dermatology Consensus Criteria), that has been present for at least 1 year before Baseline.
	• Moderate to severe atopic dermatitis defined as:
	  • Eczema Area and Severity Index ≥16 at Screening and at Baseline
	  • Investigator's global assessment 3 or 4 on a 5-point scale (at screening and Baseline)
	  • Body Surface Area involvement ≥10% at Screening and Baseline
	• Average peak pruritus score ≥3 as assessed by numerical rating scale over the last 7 days prior to Baseline
	• Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical

	treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks) • Candidate for systemic treatment

Key Exclusion criteria	• Any skin disease that, in the opinion of the investigator, including infection, would confound the diagnosis or evaluation of atopic dermatitis disease activity
	• Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days /until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
	• History of hypersensitivity to any of the study drug constituents or to drugs of similar chemical classes.
	• Risk factors for Torsades de Pointes including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia or any of the following:
	  • Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
	  • Concomitant medication(s) with a “Known Risk of Torsades de Pointes” that cannot be discontinued or replaced by safe alternative medication.
	• Resting QTcF ≥450 msec (male) or ≥470 msec (female) at screening or baseline or inability to determine the QTcF interval
	• Cardiac or cardiac repolarization abnormality
	• Subjects with pre-existing conditions that may confound ability to diagnose drug-induced liver injury (DILI) or subjects with factors that increase susceptibility to DILI
	• Participation in prior ZPL389 studies

Study treatment	ZPL389 in one of 4 dosing levels or placebo will be administered orally in capsules in the following dosing groups: • Placebo once daily • ZPL389 dose 1 once daily • ZPL389 dose 2 once daily • ZPL389 dose 3 once daily • ZPL389 dose 4 once daily
Efficacy assessments	Investigator's global assessment; Eczema Area and Severity Index
Key safety assessments	Adverse event monitoring, physical examinations including vital signs, monitoring of laboratory markers in blood and urine and electrocardiograms
Other assessments	[redacted]
Data analysis	The Multiple Comparison Procedures-Modelling methodology will be used to determine an overall dose-response signal with respect to Investigator's global assessment response at Week 16. Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.
Key words	atopic dermatitis, AD, eczema, atopic eczema, itch, pruritus, histamine 4 receptor antagonist, H4R, ZPL389

1 Introduction

1.1 Background

Atopic dermatitis (AD) is a chronic inflammatory skin disease that commonly presents first during early infancy and childhood. It is characterized by poorly defined erythema with edema, vesiculation, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage (Eichenfield 2004, Williams et al 1994). These symptoms result in a severely reduced quality of life (QOL). In particular, itching (pruritus), that continues throughout the day and worsens at night causes sleep loss and impacts everyday activities and psychosocial wellbeing (Bieber 2010, Weidinger and Novak 2016). AD is commonly associated with other atopic and inflammatory disorders, such as asthma, allergic rhinitis and food allergy. Usually the disease regresses during adolescence but symptoms may also persist into adulthood.

Two to ten percent of adults and up to 20% of children have AD, of which approximately 70% and 16%, respectively, are moderate to severe (Hanifin et al 2007, Emerson et al 1998).

Depending on the severity of the disease different therapeutic options may be proposed. The basis of AD treatment is emollients in patients of all severity stages. Additionally in patients suffering from milder forms of the disease, treatment with either topical corticosteroids (TCS) or topical calcineurin inhibitors is used. Patients suffering from more severe disease and failing to sustain response to topical agents are generally treated with phototherapy and systemic immunosuppressive drugs like cyclosporine and oral corticosteroids (Ring et al 2012, Eichenfield et al 2014, Sidbury et al 2014). Cyclosporine is approved as systemic therapy for severe AD in Europe, but renal toxicity and other adverse events (AEs) limit its long term use. Phototherapy carries the risk of future skin cancer and is not practical for many subjects. Currently the only systemic therapy approved is dupilumab (anti-Interleukin 4 Receptor alpha antibody) for treatment of moderate to severe AD, but is expected to be reserved for the most recalcitrant subjects. Thus, there is a high unmet medical need for an oral treatment in moderate to severe AD patients.

The histamine 4 receptor (H4R) is the newest member of the histamine receptor family. It is predominantly expressed on a variety of immune cells such as T cells, mast cells, eosinophils and dendritic cells. There is a large body of evidence demonstrating that the H4R is intimately linked to many inflammatory responses mediated by histamine, including chemotaxis and cell recruitment, up-regulation of adhesion molecule expression and modulation of cytokine and chemokine release (Thurmond 2015; Zhang et al 2007). In particular, there is growing preclinical evidence and emerging clinical data supporting the utility of H4R antagonists in the treatment of pruritus and atopic skin inflammation (Dunford et al 2007). For example, H4R agonists have been described to upregulate the T-helper 2 (Th2) cells and itch inducing cytokine IL-31 (Gutzmer et al 2009), contribute to Th2 polarization by suppressing IL-12 in antigen-presenting cells (Cowden et al 2010) and to induce proliferation and thymic stromal lymphopoietin (TSLP) production in human keratinocytes.

ZPL389 is a potent and selective H4R antagonist with *in vitro* binding potency of 6.2 nM and an IC_{50} value of 5.7 nM. Functional antagonism has been observed with native human H4R against a variety of endpoints associated with the chemotactic and inflammatory responses in primary human eosinophils.

1.2 Purpose

The purpose of this study is to determine the dose-response relationship of ZPL389 for key efficacy and safety parameters in order to define the most appropriate dose(s) for further development of ZPL389. Investigator's global assessment (IGA) will be assessed after treatment with 4 different ZPL389 doses or placebo administered orally once daily for 16 weeks in subjects with moderate to severe atopic dermatitis.

2 Study objectives and endpoints

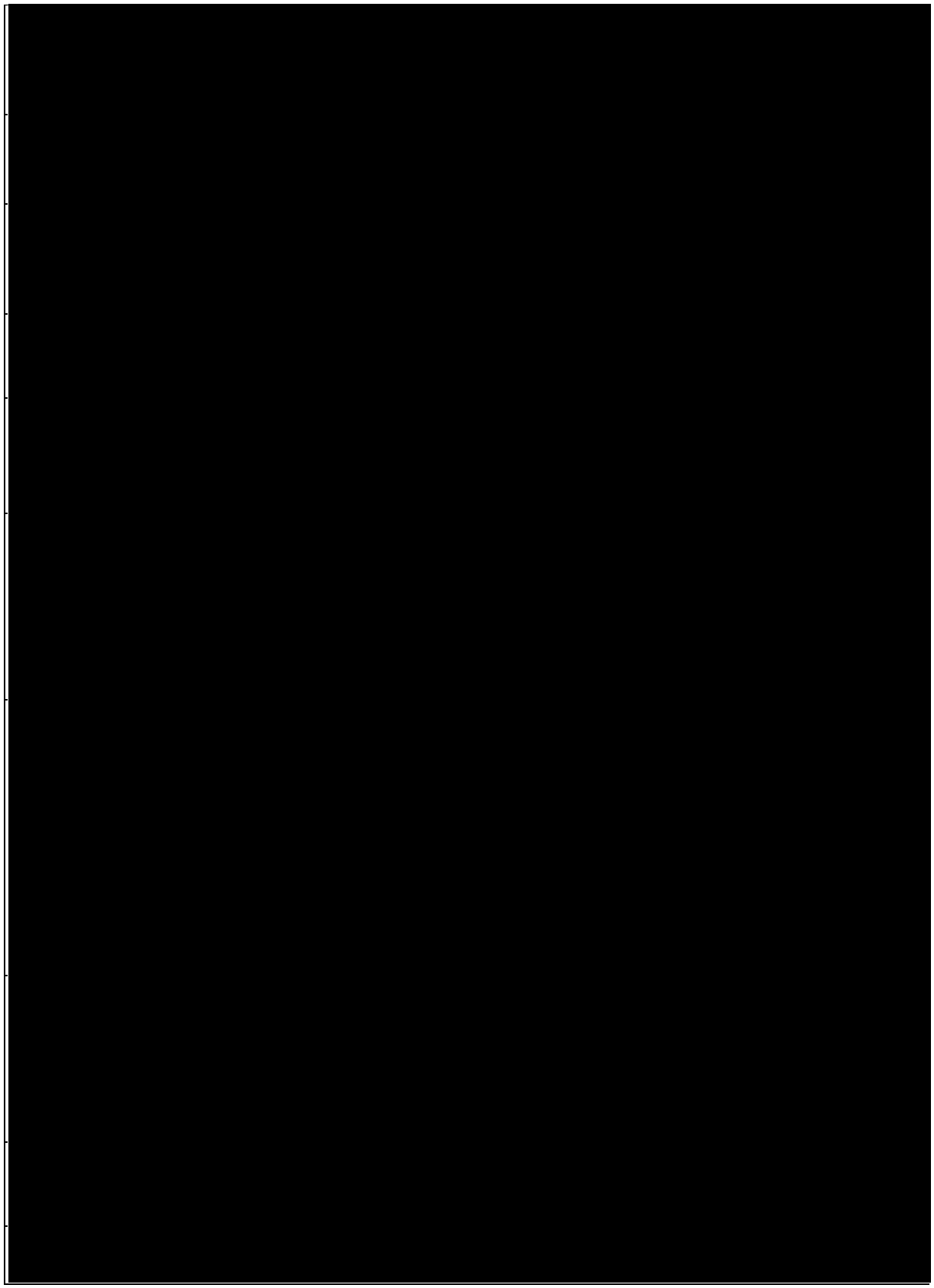
2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To characterize the dose-response relationship of ZPL389 in subjects with moderate to severe AD assessed by IGA response after 16 weeks of treatment	• IGA response at Week 16
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To characterize the dose-response relationship of ZPL389 in subjects with moderate to severe AD assessed using the percent change from Baseline in Eczema Area and Severity Index (EASI) score after 16 weeks of treatment	• Percent change from baseline EASI score at Week 16

• To evaluate the efficacy across different dose levels as assessed by EASI and IGA compared to placebo over time	• At each visit:
	  • IGA score
	  • IGA response
	  • EASI score (absolute and percent change from Baseline)
	  • EASI50 response, EASI75 response

• To assess the safety and tolerability of different doses of ZPL389 as compared to placebo	• Frequency of adverse events
[redacted]	



[redacted]

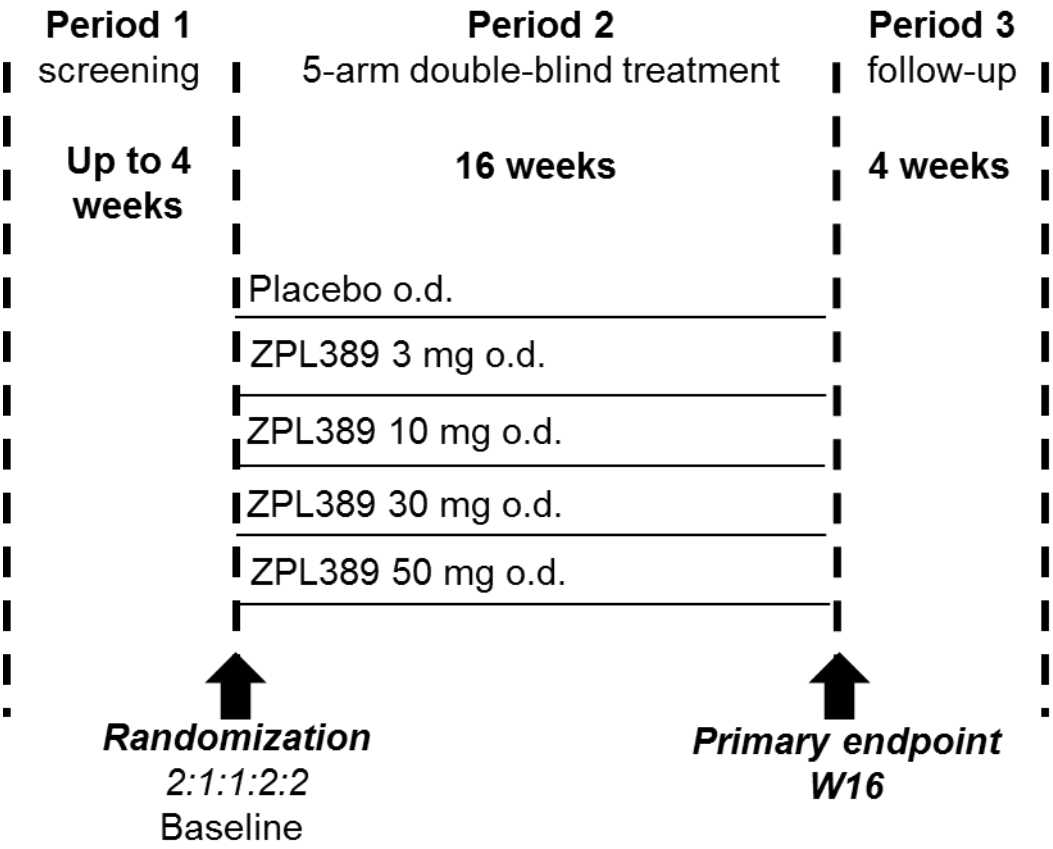
3 Investigational plan

3.1 Study design

This is a randomized, double blind, placebo controlled, parallel group, 5-arm study in at least 360 subjects with moderate to severe AD. Unbalanced randomization ratio will be utilized, to result in approximately 90 subjects randomized in each of the 30 mg/day and 50 mg/day dose arms as well as in the placebo arm, and 45 subjects in each of the 3 mg/day and 10 mg/day arms. The study consists of a screening period of up to 4 weeks (depending on current medication use and associated washout period), and a 16-week double blinded treatment period. After the end of treatment visit, subjects may be offered ongoing treatment in an extension study, or enter the 4 week treatment-free follow up period (Figure 3-1).

The total study duration will be up to 24 weeks. The details of the study design and procedures of the extension study will be described in a separate protocol.

Figure 3-1 Study design



3.2 Rationale for study design

This randomized, double-blind, parallel-group, placebo-controlled design supports the assessment of efficacy as well as safety of ZPL389 in moderate to severe AD subjects. Four dose levels were chosen to characterize the dose-response curve. An unbalanced allocation of 2:1:1:2:2 for placebo: 3 mg: 10 mg: 30 mg: 50 mg with more subjects on placebo and the higher doses of ZPL389 is chosen to increase the precision of the estimate for the treatment effect at doses in the expected efficacious dose range. The treatment length of 16 weeks (for primary endpoint) was chosen to understand when efficacy responses plateau. Additionally, this treatment length is comparable to clinical studies of other investigational treatments for moderate to severe AD patients (Simpson et al 2016).

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The doses of ZPL389 selected for this study are 3 mg, 10 mg, 30 mg, and 50 mg o.d. for 112 days.

ZPL389 is rapidly absorbed following oral administration of single and multiple doses. The estimated terminal half-life of 70-100 hours supports daily dosing of ZPL389.

The safety margins with toxicology findings and current clinical data support the use of the proposed doses. In oral toxicity studies, ZPL389 was well tolerated in rats and cynomolgus monkeys of up to 26 and 39 weeks duration, respectively. The no-observed-adverse-effect levels (NOAELs) could be established at 30 mg/kg/d in rats and 20 mg/kg/day in monkeys which result in safety margins of 20 and 60 for rats and monkeys, respectively, compared to human exposures at 50 mg dose o.d.

Interim analysis results from an ongoing phase 1 study (CZPL389A2101) which investigated single doses up to 400 mg ZPL389 and multiple doses of 50 mg/day and 100 mg/day ZPL389 (administered as drug in capsule formulation for 21 days) in 75 healthy subjects, supports the current dose selection.

Although good efficacy was observed for some endpoints in the AD proof of concept (PoC) study at 30 mg o.d., other endpoints did not show a sufficient differentiation from placebo. Given the dose of 50 mg has already been administered in healthy volunteers and the large safety margin of this dose, the maximum proposed dose in this study is 50 mg o.d.

The 30 mg dose is chosen to investigate whether there is sufficiently increased efficacy at 50 mg vs. 30 mg (the dose used in the AD PoC study). Finally, to enable exploration of the dose response curve, ½ log dose reductions of 30 mg are used, providing a mid-dose of 10 mg and a low dose of 3 mg. Overall, a more than 16-fold dose range is explored.

A dosing period of 16 weeks is expected to result in additional efficacy compared to the AD PoC study, as, unlike placebo, the efficacy of ZPL389 had not plateaued by the end of the 8-week dosing period in the PoC study.

Novartis anticipates that the proposed doses, and hence range of plasma exposures obtained from the study, will enable characterization of the dose and concentration response curves for ZPL389 in atopic dermatitis subjects.

3.4 Rationale for choice of comparator

Placebo is an appropriate comparator for the objectives of this study as it will provide the robust assessment of the efficacy and safety of ZPL389 in atopic dermatitis population.

All subjects will use a bland emollient once daily.

In addition, subjects from all treatments groups, including placebo, will have access to a standardized rescue medication if medically necessary (i.e., to control intolerable AD symptoms), as assessed by investigator and after at least 4 weeks post Baseline.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis may be performed to support decision making concerning the current clinical study or project. As a consequence the study sample size may be reduced, e.g. size of lower dose arms may be reduced by approximately 30%.

3.6 Risks and benefits

To date, 289 subjects (including asthma, psoriasis and AD patients and healthy volunteers) have been treated with at least one dose of ZPL389. The longest treatment duration to date occurred in a study of ZPL389 30 mg/day for 12 weeks in subjects with moderate to severe plaque psoriasis. In an ongoing study (CZPL389A2101), 75 healthy subjects received ascending single doses up to 400 mg ZPL389 and multiple doses of 50 mg/day and 100 mg/day for 21 days.

In the AD Phase 2a PoC study (N = 98), safety profile of ZPL389 (30 mg o.d.) was comparable to placebo and the percentages of subjects who reported adverse events were similar following 8 weeks of treatment with ZPL389 or placebo. The most common adverse events in the Phase 2a study were nasopharyngitis (12/65 [19%] subjects in the ZPL389 group and 8/33 [24%] subjects in the placebo group) and headache (7/65 [11%] subjects in the ZPL389 group and 4/33 [12%] subjects in the placebo group). No serious adverse events (SAEs) were reported following treatment with ZPL389.

Due to preclinical findings suggesting ZPL389 might prolong the corrected QT (QTc) interval when administered at several fold multiples of the intended clinical dose, 12-lead ECG monitoring was conducted in five completed clinical studies performed to date, and no clinically significant changes in ECG parameters including QTc interval prolongation have been observed following single doses of up to 48 mg and multiple doses of up to 50 mg o.d.

Interim analysis data from the ongoing study CZPL389A2101 showed clinically relevant increases of QTcF at single doses of 300 and 400 mg ZPL389 (plasma concentrations exceeding the concentration at Cmax,ss of a 50 mg o.d regimen). All elevations of QTcF and QT were asymptomatic. There were no QTcF or QT values $\geq$ 500 msec and no changes in QTcF $\geq$ 60 msec.

The concentration-QTcF analysis of the 50 mg o.d. regimen did not show QTcF results at a level of regulatory concern (i.e., an upper bound of the 90% CI of the QTcF effect for the highest clinically relevant exposure achieved with 50 mg o.d. was below 10 msec), therefore further supporting the use of a 50 mg o.d. regimen in this study.

Based on in vitro data and DDI simulations, the highest clinically relevant exposure is predicted to occur in a poor metabolizer of CYP2D6 treated with a strong inhibitor of CYP1A2. Therefore,

in the currently planned study, the scenario of highest clinically relevant exposure at a dose of 50 mg o.d. will be prevented by implementing the following measures:

1. Prohibiting the use of strong CYP1A2 inhibitors for all subjects
2. Genotyping all subjects for CYP2D6 polymorphism prior to treatment start; for those subjects identified as CYP2D6 poor metabolizers, moderate CYP1A2 inhibitors will also be prohibited

Additionally, any drug known to prolong QTc interval will be prohibited in this study. Subjects with clinically significant cardiovascular disease or close family history of long QT syndrome and subjects with QTc prolongation at screening or baseline will be excluded from this study protocol, and 12-lead ECGs will be recorded at regular intervals for subjects receiving study drug.

Preclinically, there was no signal of liver toxicity. However, due to a case indicating most probably hepatitis A infection, as a safety precaution, subjects with abnormalities of liver function will be excluded from this study, and liver function will be monitored regularly in subjects randomized into the study. In the multi-part study CZPL389A2101 in healthy volunteers, no clinically relevant changes of liver parameters in subjects treated with ZPL389 were observed.

In the GLP embryo-fetal development toxicology in rats, thoracic and abdominal situs inversus were noted in three fetuses at the highest dose tested (120 mg/kg/day). The dose of 120 mg/kg/day corresponds to 22 to 27 fold exposure over the human exposure with 50 mg o.d. Such findings can occur spontaneously but are rare. Minor maternal toxicity was seen at the same dose 120 mg/kg/day, therefore maternal and fetal NOAEL in this study in rats was considered to be 60 mg/kg/day (12 to 17 fold exposure over the human exposure with 50 mg o.d.). In the GLP embryo-fetal development toxicology in rabbits, no effects were noted, including at the highest dose tested, 15 mg/kg/day. ZPL389 should not be administered to females of child-bearing potential in long-term clinical studies unless protocol-specified contraceptive measures are implemented. Sexually active males and females must use appropriate contraception as indicated in the clinical protocol. Women of child-bearing potential (WOCBP) will be required to have monthly serum pregnancy tests. It is unknown whether ZPL389 is excreted in human breast milk and hence ZPL389 should not be administered to lactating females.

Full details of the preclinical and clinical data are summarized in the Investigator's Brochure (IB). There are unknown risks to ZPL389 which may be serious.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, including a data monitoring committee (DMC) and study drug discontinuation rules. Considering efficacy observed in the PoC study, overall safety observed in studies to date, and the absence of approved oral agent for AD, the benefit/risk appears to be positive.

4 Population

The study population will consist of female and male subjects aged 18 years or older with moderate to severe AD. It is planned to randomize approximately 360 subjects globally. The

screen failure rate is estimated to be 30% and thus a total of around 515 subjects are expected to be screened in approximately 110-140 investigational sites.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Females and males aged 18 years or older at the time of Screening
3. Chronic AD; according to American Academy of Dermatology Consensus Criteria (Eichenfield et al 2014), that has been present for at least 1 year before the baseline visit.
4. Moderate to severe AD defined as:
   - Eczema Area and Severity Index (EASI) ≥16 at Screening and at Baseline
   - IGA 3 or 4 on a 5-point scale (where 3 is moderate and 4 is severe) at Screening and Baseline
   - BSA involvement ≥10% at Screening and Baseline
5. Average peak pruritus score ≥3 as assessed by NRS over the last 7 days prior to Baseline
6. Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications for AD or for whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks).
7. Candidate for systemic treatment
8. Have applied a stable dose of bland topical emollient once daily for at least the 7 consecutive days immediately before the baseline visit
9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, diary completion and other study procedures.

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Any skin disease that, in the opinion of the investigator, would confound the diagnosis or evaluation of AD disease activity (e.g., Netherton Syndrome, Cutaneous T-Cell Lymphoma, extensive contact dermatitis, chronic actinic dermatitis)
2. Current active skin infection at Baseline, that in the opinion of the investigator, would confound the diagnosis or evaluation of AD disease activity
3. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days /until the expected PD effect has returned to baseline, whichever is longer.
4. History of hypersensitivity to any of the study drug constituents or to drugs of similar chemical classes.
5. Subjects taking medications prohibited by the protocol (see Table 5-1)
6. Risk factors for Torsades de Pointes (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia or any of the following:
   - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome

- Concomitant medication(s) with a "Known Risk of Torsades de Pointes" that cannot be discontinued or replaced by safe alternative medication.

7. Resting QTcF ≥450 msec (male) or ≥470 msec (female) at Screening or Baseline or inability to determine the QTcF interval
8. Cardiac or cardiac repolarization abnormality, including any of the following:
   - History of myocardial infarction, angina pectoris, or coronary artery bypass graft within 6 months prior to starting study treatment
   - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II and third degree AV block)
9. Subjects with pre-existing conditions that may confound ability to diagnose drug-induced liver injury (DILI) or subjects with factors that increase susceptibility to DILI, including but not limited to:
   - Ongoing liver disease
   - Cirrhosis, compensated or decompensated
   - History of hepatitis B or C
   - Positive hepatitis B surface antigen (HBsAg), antiHB core antigen antibody (anti-HBc) or anti-HB surface antigen antibody (anti-HBs) or positive hepatitis C test result (Subjects positive for anti-HBs after Hep B vaccination but negative for HBsAg and anti-HBc are eligible; Table 16-1)
   - Hepatitis A or B vaccination in last 3 months
   - Unhealthy alcohol use
   - Known gallbladder or bile duct disease
   - Acute or chronic pancreatitis
   - Acute decompensated heart failure
   - Chronic treatment with medication with hepatotoxic potential
10. Subjects who have a laboratory abnormality at Screening as follows:
    - ALT/AST/ALP above 1.5 upper limit of normal (ULN), or TBL above upper limit of normal (ULN)
    - Total white blood cell count (WBC) <2.5 x 10^9cells/L
    - Absolute neutrophil count (ANC) <1.5 x 10^9/L
    - Hemoglobin <11.0 g/dL
    - Platelets <100.0 x 10^9/L
    - Potassium or magnesium below normal range
    - Estimated Glomerular Filtration Rate by the Modification of Diet in Renal Disease (MDRD) equation <60 mL/minute/1.73 m^2

    Note: One central lab retest will be allowed for lab abnormalities outside the above mentioned respective cut-off criteria during the screening period, if the investigator believes the abnormality is transient and not clinically significant
11. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for skin Bowen's disease, completely

treated and resolved non-metastatic squamous or basal cell carcinoma of the skin or actinic keratosis that has been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)

12. Past medical history record of, or current infection with, human immunodeficiency virus (HIV)
13. Any surgical, medical (e.g., uncontrolled hypertension, heart failure or diabetes), psychiatric or additional physical condition that the Investigator feels may jeopardize the subject in case of participation in this study
14. Pregnant or nursing (lactating) women
15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using required methods of contraception during dosing and for 4 weeks after stopping of investigational medication. Required contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (bilateral oophorectomy with or without hysterectomy, total hysterectomy or tubal ligation) at least six weeks before taking investigational drug. In case of oophorectomy alone, the reproductive status of the woman must have been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Placement of an intrauterine device (IUD) or intrauterine system
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that are considered highly effective (i.e. failure rate <1%), i.e. for oral contraceptives only hormonal contraception associated with inhibition of ovulation is allowed.
      In the case of this method, **the addition of a male condom is required.**

      In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

      In subjects who are poor CYP2D6 metabolizers, hormonal contraception is not allowed and other contraceptive options as per the protocol should be followed.

    In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

16. Sexually active males unless they use a condom during intercourse while taking drug and for 4 weeks after stopping investigational medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.
17. Prior exposure to ZPL389 treatment.

[redacted]

4.3 Inclusion criteria [redacted]

Subjects eligible for inclusion in this substudy must fulfill **all** of the following criteria:

10. Subjects eligible for the main study who consent to participate in the substudy
11. Subjects residing in a country where the substudy will be conducted.

4.4 Exclusion criteria [redacted]

Subjects fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this substudy:

[redacted]

5 Treatment

5.1 Treatment assignment and randomization

At Baseline, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject is eligible according to the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the subject. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject

randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

In the proof of concept study, response to treatment was related to the Baseline IGA score and therefore randomization will be stratified by Baseline IGA moderate (3) or severe (4). In addition, randomization will be stratified by geographical region.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Group.

5.2 Study treatment

5.2.1 Investigational and control drugs

ZPL389 and placebo will be administered in hydroxypropyl methylcellulose capsules. The capsule's size is "0" (21.7 x 7.6 mm) and is pink in color.

ZPL389 will be dispensed as 3 mg, 10 mg, 30 mg and 50 mg capsules.

5.2.2 Additional treatment

The use of a bland emollient is required throughout the study and to be applied once a day on the entire body. **Subjects should use the same emollient throughout the study. To allow adequate assessment of skin dryness, emollient should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.**

During the screening period, investigators are to evaluate the emollient used by the subjects to ensure it is a bland emollient, i.e. emollients not containing ingredients such as ceramides, lactic acid, urea, α-hydroxy- or fruit acids, vitamins A or D.

Subjects are requested to enter their daily use of emollients in the e-diary described in Section 6.6.1.6.

5.3 Treatment arms

Subjects will be assigned at Baseline to one of the following 5 treatment arms in a ratio of 2:1:1:2:2.

- Placebo o.d.
- ZPL389 3 mg o.d.
- ZPL389 10 mg o.d.
- ZPL389 30 mg o.d.
- ZPL389 50 mg o.d.

5.4 Treatment blinding

Subjects, investigator staff, and persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until database lock (note that if the patient rolls over into the extension study, this will be at the completion of the double blind period of the extension study) using below methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study except in the case of subject emergencies (see Section 5.5.9). (2) the identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Data analysts and core clinical trial team members will remain blinded to the identity of the treatment from the time of randomization until database lock of the core study using similar methods mentioned above. In case an interim analysis is performed, designated Novartis team members will be unblinded, however core Novartis team reviewing study data will remain blinded until the final database lock.

Unblinding will only occur in the case of subject emergencies (see Section 5.5.9), and at the completion of the study. [redacted]

5.5 Treating the subject

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Subject numbering

Each subject is uniquely identified by a Subject Number assigned by Novartis. The Subject number is composed of a site number and a sequential number. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next sequential number available in the electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site must select the Case Report Form (CRF) book with a matching Subject Number in the EDC system to enter data.

If the subject fails to be treated for any reason, the IRT must be notified within 2 days that the subject was not treated. The reason for not being treated will be entered on the appropriate CRF.

Subjects can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the subject.

Mis-randomized subjects are defined as cases where IRT randomization was performed by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 5 treatment arms and a specific dose. Investigator staff will identify the study drug package(s) to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors. Subjects will be asked to return all unused study treatment at each visit and at the end of treatment or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Subjects are requested to enter their daily use of emollients in the e-diary. Rescue medication is discussed in Section 5.5.6.

5.5.4 Instructions for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

ZPL389 will be provided as 3 mg, 10 mg, 30 mg and 50 mg powder in capsules. Placebo will be provided as visually matched capsules. Bottles of capsules will be dispensed at study visits occurring at Baseline and every 4 weeks thereafter. All study drugs will be supplied in identical bottles and will be the same color and appearance, thereby maintaining double-blind conditions.

Study medication will be supplied to the subject at:

- Baseline visit (Day 1): 1 bottle of ZPL389 or matching placebo
- Week 4 (Day 29): 1 bottle of ZPL389 or matching placebo
- Week 8 (Day 57): 1 bottle of ZPL389 or matching placebo

• Week 12 (Day 85): 1 bottle of ZPL389 or matching placebo

Note: Investigators must check the number of doses already taken by the subject, and ensure that the Week 16 visit is scheduled such that the subjects take approximately 112 capsules in total.

Subjects must be instructed to take one capsule per day at the same time every day preferably in the morning (e.g. every day at 8 am). The subject will record the intake of study medication on a daily basis on the subject e-diary. On days of a scheduled study visit, subjects must be instructed to:

- **bring all current study medication with them to the visit**
- **not take the investigational treatment at home on the day of a study visit but must take it when instructed by study personnel at the investigational site** [redacted]

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments are not permitted. Treatment might be interrupted as per guidance in the safety monitoring Sections 14 and 15.

Changes must be recorded on the appropriate CRF.

5.5.6 Rescue medication

Only after four weeks post Baseline and only if medically necessary (i.e., to control intolerable AD symptoms), as assessed by investigator, rescue treatment for AD may be provided to study subjects. The rescue therapy may not be dispensed as a precaution. If the need for rescue therapy arises between scheduled study visits, the subject needs to come for an unplanned visit for the investigator to assess the subject.

The following rescue medication will be provided/reimbursed by Novartis: mometasone furoate cream 0.1% (TCS). The rescue medication may only be used to treat AD symptoms. If patients have tolerance issues with mometasone furoate cream 0.1% or in countries where mometasone furoate cream 0.1% is not available for the relief of AD symptoms or its use is restricted by its label, an alternative TCS of similar potency will be provided. If and only when the use of mometasone furoate cream 0.1% is not deemed appropriate for problem areas, e.g., face, neck, intertriginous and genital areas, then hydrocortisone 2.5% ointment or topical calcineurin inhibitors could be used instead in these areas only. Any other TCS/TCI use is prohibited.

Investigators must remind subjects that they should use rescue medication only if really needed and only when instructed by the investigator because the use of rescue medication may affect the validity of study results negatively. Rescue medication **use must be stopped as soon as not needed anymore as assessed by the investigator.**

Subjects should allow adequate time for absorption after each rescue medication **application before applying an emollient and record their** rescue medication **use in the e-**

diary (see Section 6.6.1). At each study visit, after a subject was given rescue medication, the subject will have to bring the rescue medication tube/ container to the site and the investigator will review the e-diary. Rescue medication tubes/container will be weighed at the time of dispensing and every subsequent visit and the weight used recorded in the appropriate CRF.

5.5.7 Concomitant medication

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the appropriate CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in the below table is NOT allowed during the period specified below in Table 5-1.

Table 5-1 Prohibited medication/therapy

Medication/therapy	Prohibited period	Action taken
Topical corticosteroids (TCS) Topical calcineurin inhibitors (TCI) Other topical treatment for AD such as crisaborole, tar etc. Initiation of treatment of AD with prescription moisturizers or moisturizers containing ingredients such as ceramides, lactic acid, urea, α-hydroxy- or fruit acids, vitamins A or D	a) Within 1 week prior to Baseline b) Treatment period c) Follow up period	a) Delay randomization to achieve 1-week wash out or discontinue subject from trial b) Discontinue prohibited medication and continue study treatment OR If the subject meets criteria for rescue medication and only after 4 weeks post Baseline, follow instructions in Section 5.5.6** c) Discontinue prohibited medication, unless patient is in the follow up period after early treatment discontinuation
Systemic immunosuppressive treatments* including but not limited to systemic corticosteroids (e.g., i.v., i.m. or oral), cyclosporine, tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, JAK inhibitors, apremilast, biologic therapies (like dupilumab, etanercept, adalimumab, infliximab, omalizumab), chinese traditional medicine	a) Within 4 weeks prior to Baseline for non biologics / within 3 months prior to Baseline for biologic treatments or within 5 half-lives of Baseline, whichever is longer	a) Discontinue subject from trial and rescreen subject after wash-out and if recruitment period is still ongoing

Medication/therapy	Prohibited period	Action taken
	b) Treatment period	b) Discontinue prohibited medication and continue study treatment unless there is a specific safety risk for the subject, in the opinion of the investigator in which case study treatment must be discontinued
	c) Follow up period	c) Discontinue prohibited medication
Oral antihistamines (H1 antihistamines are allowed if the subject is on a stable dose or used short term to, for example, treat allergies)	a) Within 1 week prior to Baseline	a) Delay randomization to achieve 1-week wash out or discontinue subject from trial
	b) Treatment period	b) Discontinue the prohibited therapy, and continue study treatment unless there is a specific safety risk for the subject, in the opinion of the investigator in which case study treatment must be discontinued
	c) Follow up period	c) Discontinue prohibited medication
Phototherapy or tanning booths Bleach baths	a) 4 weeks prior to Baseline	a) Discontinue subject from study and rescreen subject after wash-out if the recruitment period is still ongoing
	b) Treatment period	b) Discontinue prohibited medication/therapy, and continue study treatment
	c) Follow up period	c) Discontinue prohibited medication
Any investigational treatment	a) Within 5 half-lives of Baseline or until the expected pharmacodynamic effect has disappeared, whichever is longer	a) Discontinue subject from trial and rescreen subject after wash-out if the recruitment period is still ongoing
	b)Treatment period	b) Discontinue subject from study treatment
	c) Follow up period	c) Discontinue prohibited medication
Any drug known to prolong QTc interval (See https://crediblemeds.org/ for details as well as protocol supplementary guidance) Drugs known to be hepatotoxic (please see protocol supplementary guidance)[#]	a) Within 5 half-lives of Baseline or until pharmacodynamic effect has disappeared, whichever is longer	a) Discontinue subject from study and rescreen subject after wash-out if the recruitment period is still ongoing
	b) Treatment period	b) Discontinue study treatment

Medication/therapy	Prohibited period	Action taken
Strong (Potent) CYP1A2 inhibitors (see protocol supplementary guidance) for all subjects For subjects that are poor CYP2D6 metabolizers, strong and moderate CYP1A2 inhibitors (see protocol supplementary guidance)	c) Follow up period	c) Discontinue prohibited medication (unless taken 4 weeks after early treatment discontinuation where it can be allowed if medically necessary)
Patients participating in [redacted] must not take [redacted]	a) Within 2 weeks of Baseline b) Treatment period c) Follow up period	a) Patient is not eligible for substudy and will not participate b) Discontinue prohibited treatment c) Discontinue prohibited medication

*CS nasal sprays and eye drops are not considered systemic immunosuppressive treatment

**Rescue therapy used as per Section 5.5.6 (only if medically necessary i.e., to control intolerable AD symptoms, as assessed by investigator and only after at least 4 weeks post Baseline) is not considered a prohibited medication.

short course of ibuprofen or topical NSAID may be allowed if investigator is of the opinion that it is in the best interest of the subject and that no hepatotoxicity is expected.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

In addition, oral and written information on how to contact his/her backup in cases of emergency, or when he/she is unavailable, must be provided to the subject to ensure that un-blinding can be performed at any time.

The subject must be followed up and continue the study visit schedules.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

The study will be completed once all subjects have either entered the extension trial or have completed the Week 20 visit.

Subjects may be offered participation in an extension study. The details of the study design and procedures of the extension study will be described in a separate protocol. If the subject does not enter the extension study, the investigator and/or referring physician must ensure that continuing care is provided.

When the subject has completed all scheduled study assessments or prematurely withdrawn from the study, the investigator must contact the IRT to record the subject completion /discontinuation and complete applicable CRF.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would negatively impact the subject or in the event the subject is unwilling or unable to comply with study requirements.

Study treatment must be discontinued under the following circumstances:

- Subject wishes to withdraw consent
- Pregnancy (Section 7.7)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study participation might result in a safety risk to the subject
- QTcF >500 msec, confirmed by repeat ECG measurements
- QRS >110 msec and increase >25% from Baseline (Day 1)
- Cardiac abnormalities of CTCAE v4.03 severity grade ≥2, including:
    - Resting heart rate <60 or >100 bpm confirmed by repeat measurement and associated with symptoms, indicating medical intervention
    - Ventricular fibrillation, or any clinically significant cardiac arrhythmia
    - New complete heart block (Grade III AV block)
    - Second degree AV block Mobitz type II associated with symptoms, indicating medical intervention
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Liver and renal events requiring treatment discontinuation as per Table 14-2 and Table 15-1
- Laboratory abnormalities indicating blood and lymphatic system disorders of CTCAE v4.03 of severity grade ≥2 including:
    - Anemia: Hemoglobin <10 g/dL

- Febrile neutropenia (ANC <1000/mm^3 with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of ≥38 ºC (100.4 ºF) for more than 1 hour
- Leukocytes >100,000/mm^3
- Lymph node pain of at least moderate intensity
- Spleen disorder requiring prophylactic antibiotics
- Thrombotic thrombocytopenic purpura

If discontinuation of study treatment occurs, the subject should not receive additional doses. Subjects should remain in the study and be followed at least until the adverse event resolves / stabilizes, or until the end of the study, whichever is longer. I.e. After study treatment discontinuation, the subject should remain in the study and attend study visits as normal in Table 6-1 (without contacting IRT /drug dispensing). Subjects who discontinue treatment and wish to discontinue the study should at a minimum return for the End of Treatment visit (Week 16 visit) and the Follow up visit (Week 20 visit), as detailed in Table 6-1, and assessment should be completed and recorded in the appropriate CRF. The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the CRF.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore,

and

- Does not allow further collection of personal data

In this situation, the investigator must make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. Prior to withdrawal, evaluation should be made as detailed in the assessment table (End of Treatment Week 16 visit). All e-diaries and devices and study medication must be returned to the site at this visit.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For United States and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union and Rest of World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason.

Reasons for early termination:

- Unexpected, significant or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. If the study is terminated prematurely the investigator or treating physician must ensure appropriate ongoing care is provided to the patient. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments/actions and indicates with an "X" or "S" at which visits they are performed.

Subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue from the study should have at the time of discontinuation all of the assessments listed for the End of Treatment Week 16 visit, and a Follow-up Week 20 visit. All e-diaries and devices and study medication must be returned to the site at this visit. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Subjects should be reminded to be fasting for at least 3 hours before the visits and to bring their medication and their e-diaries. They should not eat at least until the last ECG is performed.

Table 6-1 Assessment Schedule

Period	Screening	Treatment							Follow-up (EOS/PSW)	Unplanned
Visit Day	**-28 to -1**	**1**	**15**	**29**	**43**	**57**	**85**	**113[1]**	**141**	**-**
Weeks	**-4 to -1**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**0**
Informed consent	X									
Demography, AD medical history, Medical history/current medical conditions, Smoking history	X									
Inclusion / Exclusion criteria	X	X								
Randomization		X								
Physical Examination	S	S	S	S	S	S	S	S	S	S
Electrocardiogram (ECG)[2]	X	X (predose AND 2h postdose)[3]	X	X (predose AND 2h postdose)[3]	X	X	X	X[3]	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Body Height	X									
Body Weight	X	X		X		X	X	X	X	
Hepatitis screen, HIV screen	X									
Hematology, Clinical Chemistry, Urinalysis	X	X	X	X	X	X	X	X	X	X
[redacted]										
Pregnancy Test (Serum)	X	X		X		X	X	X	X	
Pregnancy Test (Urine)		S								
[redacted]										
[redacted]										
[redacted]										
[redacted]										
Concomitant medications/ Surgical or Medical Procedure	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X

Period	Screening	Treatment							Follow-up (EOS/PSW)	Unplanned
Visit Day	-28 to -1	1	15	29	43	57	85	113[1]	141	-
Weeks	-4 to -1	0	2	4	6	8	12	16	20	0
[redacted]										
Patient e-Diary daily entry[4]	X									
Patient e-Diary Review		X	X	X	X	X	X	X	X	X
[redacted]										
IGA, EASI (incl. BSA), [redacted]	X	X	X	X	X	X	X	X	X	X
Drug dispensation[5]		X		X		X	X			
Drug accountability				X		X	X	X		
Dosing at site[6]		X	X	X	X	X	X			
[redacted]										
[redacted]										
Study Disposition	X									

[1]Visit must be the day after the last day of dosing i.e. Day 113; End of treatment visit (EOT) or treatment discontinuation (TD)

[2]All ECGs are to be performed under fasted conditions (subjects should fast at least 3 hours before the site visit and remain fasted until the last ECG is done). ECG should be done after 10 min rest in supine position, followed by vital signs while supine and then blood samples

[3]Triplicate standard 12-lead ECGs will be performed at: Baseline (triplicate before intake of drug and triplicate 2 hours post dose), Week 4 (triplicate before intake of drug and triplicate 2 hours post dose), and at Week 16 (triplicate before intake of drug). Single standard ECGs should be done at all other visits.

[4]Starting 1 week prior to Baseline. The investigational site staff must make a phone call to the patient to remind them to switch on the device and start completion. Patient e-Diary will include [redacted] daily use of emollients, study drug and rescue therapy (if any).

[5]Subjects should be instructed to take study medication every day at the same time preferably in the morning except on study visit days. The subject will record the intake of study medication on a daily basis on the subject e-diary.

[6] On days of a study visit, subjects should not take the investigational treatment at home; instead they will take it when instructed by study personnel at the investigational site [redacted].

Note: The use of a bland emollient is required throughout the study and to be applied once a day on the entire body. Subjects should use the same emollient throughout the study. To allow adequate assessment of skin dryness, emollient should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit. Tube/container of rescue medication (if any; only when medically justified) will be weighed at the time of dispensing and at every subsequent visit while the rescue medication is used and the weight used recorded.

Period	Screening	Treatment							Follow-up (EOS/PSW)	Unplanned
Visit Day	-28 to -1	1	15	29	43	57	85	113[1]	141	-
Weeks	-4 to -1	0	2	4	6	8	12	16	20	0

[redacted]

Note: Patient reported outcomes must be done before physician assessments (IGA, then EASI and BSA[redacted])

EOS = End of Study. PSW = Premature study withdrawal. X = will be captured in systems for study data collection; S = source capture only

[redacted]

6.1 Information to be collected on screening failures

All subjects who have signed informed consent but not entered into the next period will have the disposition, demographics, inclusion/exclusion, informed consent, rescreening, withdrawal of consent (if subject withdrew consent) and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator or primary care physician and collected only in the source data.

6.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: age, sex, race, ethnicity, smoking history, relevant medical history/family history or current medical condition present before signing informed consent. When possible, diagnoses and not symptoms will be recorded. [redacted]

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature. Information about characteristics and history of subjects' AD including previous treatment received will be collected.

6.2.1 Screening for HIV/Hep B and Hep C

- All subjects will be screened for hepatitis B surface antigen (HBsAg), anti-HBs, and anti-HBc. Subjects testing positive for any of the serologic markers will not be eligible for randomization, with the exception of anti-HBs due to previous vaccination against Hep B (unless vaccination was in the past 3 months). Table 16-1 provides detailed Hep B serology result interpretations.
- Screening for hepatitis C will be based on hepatitis C virus antibodies; if the qualitative test result is positive, it will be verified by a second technique (e.g. HCV RNA quantification)
- Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Results will be available as source data and will not be recorded within the CRF. All samples will be shipped to the central laboratory.

6.3 Treatment exposure and compliance

6.3.1 ZPL389 / placebo

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording capsule counts from the previously dispensed container. This information should be captured in the source document at each designated visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Subjects must be requested to record in the e-diary their intake of study medication on a daily basis.

Study personnel will review the e-diary entries at each visit for study drug intake and discuss with patient any missed doses. Study personnel will also review the amount of study medication returned by the subject. The total number of doses of study drug intake since the last dispensing visit will be recorded in the appropriate CRF based on the returned study medication and discussion with the patient.

6.3.2 Rescue medication and emollient

Subjects are requested to record in the e-diary their use of emollient. If the subject needed rescue medication and it was dispensed by the investigator, the subject needs to enter rescue medication use on a daily basis in the e-diary.

In addition, Investigators will weigh the rescue medication container at the time of dispensing and at the time of return at the next study visit. The information will be recorded in the appropriate CRF.

6.4 Efficacy

The investigator assessments should be performed by the same member of study site staff throughout the study. Adequate time should be scheduled allowing for a complete examination.

The IGA, EASI, [redacted] evaluations require a full-body examination - subjects must be undressed. Observations must also be made in a well-lit area.

Assessments performed by the investigator are to be conducted after the subject has completed the on-site reported outcome assessments, and should be performed in the following order: IGA, then EASI [redacted].

6.4.1 Appropriateness of efficacy assessments

The efficacy measurements are standard for this indication (Eichenfield et al 2014).

6.4.2 IGA

The IGA rating scale is used to determine the severity of AD symptoms and clinical response to treatment. It reflects a subject's overall disease severity for the whole body based on a 5-point scale. The 5-point scale includes: clear, almost clear, mild, moderate, and severe disease. It is a static scale and does not refer to previous status of the subject. The Investigator or trained qualified designee will complete the IGA assessment on each of the visits as outlined in the assessment schedule. Whenever possible, the IGA assessments should be performed by the same evaluator throughout the study. Please, see Section 17 for details.

6.4.3 EASI

The EASI (Eczema Area and Severity Index) will be used to make an assessment of the extent and severity of AD (Hanifin 2001). The Investigator or trained qualified designee will complete the EASI assessment on each of the visits as outlined in the assessment schedule. Whenever possible, the EASI assessments should be performed by the same evaluator throughout the study.

Each body region (head/neck [H], upper limbs [UL], trunk [T], and lower limbs [LL]) will be assessed for:

- Severity of AD: the average degree of the following key signs of AD (erythema, induration/papulation, excoriation, and lichenification) will each be assigned a score of 0, 1, 2 or 3 indicating none (0), mild (1), moderate (2), and severe (3) expression of the clinical sign, as indicated in Table 6-3 EASI: severity descriptions.
- Extent of AD: Based on the extent of AD in a particular body region (when each body region is considered as a whole or 100%), an Area score will be assigned to that body region.

Please note:

- Only inflamed areas should be included in the assessment, dry skin or post inflammatory pigmentation changes should not be included.
- The neck is assessed as part of the head region.
- The axillae and groin are assessed as part of the trunk.
- The buttocks are assessed as part of the lower limbs.

For a calculation of EASI score (ranging from 0 to 72), please see Table 6-4.

Calculation of BSA (total body surface area affected by AD): percentage of each body region affected by AD will be multiplied by its respective body region corresponding factor (0.1 for head, 0.3 for trunk, 0.2 for upper limbs and 0.4 for lower limbs).

Total BSA affected by AD = 0.1xHead area % + 0.2xUpper limbs area % + 0.3xTrunk area % + 0.4xLower limbs area %.

Table 6-3 EASI: severity descriptions

Sign score	Grading	Description
Erythema (E)		
0	None	N/A
1	Mild	Faintly detectable erythema: very light pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep/dark red
Induration / Papulation (P)		
0	None	N/A
1	Mild	Barely perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Excoriations (Ex)		
0	None	N/A
1	Mild	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions
Lichenification (L)		
0	None	N/A

1	Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a visible crisscross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated crisscross pattern

Table 6-4 EASI calculation

Body region	Erythema (E)	Induration / Papulation(P)	Excoriation (Ex)	Lichenification (L)	Area score (A)	*EASI calculation*
Head & neck (H)	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0= 0% 1= >0 - <10% 2=10% to <30% 3=30% to <50% 4=50% to <70% 5=70% to <90% 6=90% to 100%	(E+P+Ex+L) x A x 0.1
Trunk (T)	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0=0% 1=>0 - <10% 2=10% to <30% 3=30% to <50% 4=50% to <70% 5=70% to <90% 6=90% to 100%	(E+P+Ex+L) x A x 0.3
Upper limbs (UL)	0= none 1= mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0= none 1= mild 2=moderate 3= severe	0= none 1= mild 2=moderate 3=severe	0= 0% 1= >0 - <10% 2=10% to <30% 3=30% to <50% 4=50% to <70% 5=70% to <90% 6=90% to 100%	(E+P+Ex+L) x A x 0.2
Lower limbs (LL)	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3=severe	0=none 1=mild 2=moderate 3= severe	0= 0% 1= >0 - <10% 2=10% to <30% 3=30% to <50% 4=50% to <70% 5=70% to <90% 6=90% to 100%	(E+P+Ex+L) x A x 0.4
EASI score =						***sum of the above 4 scores***

[redacted]

[redacted]

6.5 Safety

In addition to the below listed safety assessments, safety monitoring must be done at every visit as per Section 7 as well as review of concomitant medications with reference to prohibited medications (Table 5-1). The safety assessments and monitoring is in accordance with the risks associated with ZPL389 and/or unknown information.

6.5.1 Physical exam

A physical examination, including general appearance, will be performed at every visit. If indicated, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator. If possible, assessments for an individual subject should be performed by the same member of the study site staff throughout the study.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the subject signing informed consent must be included in the medical history CRF. Significant findings made after the signing of the informed consent which meet the definition of an AE must be recorded on the AE CRF.

6.5.2 Body Weight and height

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at the visits specified in the table of assessments.

Height in centimeters (cm) will be measured at the visit specified in the assessments schedule.

6.5.3 Electrocardiogram (ECG)

ECGs will be analyzed centrally and performed with ECG machines supplied by the central provider.

ECGs should be done in fasting conditions (subjects should fast for at least 3 hours before the site visit) and after 10 minutes rest in the supine position. The sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs and then blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Standard 12-lead ECGs will be performed as indicated in the assessment schedule; triplicates standard ECG at Baseline, Week 4 and Week 16 visits and single standard ECGs at all other visits. Subjects must remain fasted until the last ECG is performed.

In the event that the central cardiologist reports that an ECG is abnormal, then the investigator must comment as to whether the ECG abnormality is either clinically significant or clinically insignificant. If necessary, a local cardiologist may be consulted.

Clinically significant abnormalities should be recorded on the relevant section of the appropriate CRF.

6.5.4 Vital Signs

Measurements will include pulse rate, supine systolic and diastolic blood pressure.

On visits where an ECG is also being performed, the blood pressure measurement should be done after the ECG measurements while the subject is in the supine position. Pulse rate (heart rate) will be done as part of the ECG measurement, if taken at the visit at which ECG is done.

After the subject has been resting in supine position for approximately 10 minutes, systolic and diastolic blood pressure will be measured twice using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat measurements will be made at 1 to 2 minute intervals and the mean of the two measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

6.5.5 Laboratory evaluations

A central laboratory will be used for analysis of all blood specimens detailed in this section, unless otherwise specified. Samples will be collected according to the assessment schedule. Details on the collections, shipment of samples, and reporting of results by the central laboratory will be provided to Investigators in the central laboratory manual.

6.5.5.1 Clinical Chemistry

The chemistry panel will include: albumin, alkaline phosphatase (ALP), total bilirubin (TBL), calcium, chloride, total cholesterol, LDL-cholesterol, HDL-cholesterol, creatinine, creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (γ-GT), glucose, sodium, potassium, inorganic phosphorus, total protein, lactate dehydrogenase (LDH), triglycerides, magnesium, blood urea nitrogen (BUN), and uric acid. Estimated creatinine clearance will be calculated using the MDRD formula. Lipase and amylase will be included at Screening and Baseline. PT/INR (Prothrombin time/ International Normalized Ratio) must be included in unscheduled visits.

If the TBL concentration is increased above 1.5 x ULN, direct and indirect reacting bilirubin should be differentiated.

6.5.5.2 Hematology

Hemoglobin, hematocrit, red blood cell count, WBC count with differentials and platelet count will be measured.

6.5.6 Pregnancy Test

For all WOCBP, a serum pregnancy test is required at Screening, Baseline and at monthly intervals during treatment (at scheduled visits). A serum pregnancy test will also be performed at the end of the study. Additionally, at Baseline a urine pregnancy assessment should be done and the result must be evaluated prior to randomization but only captured on source documents.

6.5.6.1 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes will be performed.

If dipstick measurement results are positive (abnormal), results will be captured in the CRF. Microscopy must be assessed following an abnormal dipstick test.

6.6 Other assessments

6.6.1 Clinical Outcome Assessments

[redacted] All the PROs should be completed by the subject before they see the study physician (investigator or designee) who will perform the investigator assessments. Exceptionally, if the electronic device is not working, the questionnaires might be completed on paper.

[redacted]

[redacted]

6.6.1.6 Patient e-diary

Subjects will be asked to complete an e-diary. The patient e-diary will be dispensed at Screening to all subjects. They will complete entries on a daily basis at home starting one week prior to

their scheduled Baseline visit. The device will remind the subjects to complete the questions however, the site staff must make a telephone call to each subject one week prior to their scheduled Baseline visit to remind them to charge and switch on the device and to complete the e-dairy on a daily basis in order for the inclusion criterion 5 to be evaluated on the day of Baseline. Subjects must bring their e-diaries with them to every scheduled visit. The patient e-diary will be checked by a designated study staff member at each visit; in case of incomplete e-dairy entry, the study site staff will counsel the subject on the correct use and frequency of the patient e-diary.

Daily entries starting 1 week prior to the scheduled Baseline visit:

- Emollient use (see Section 5.2.2)

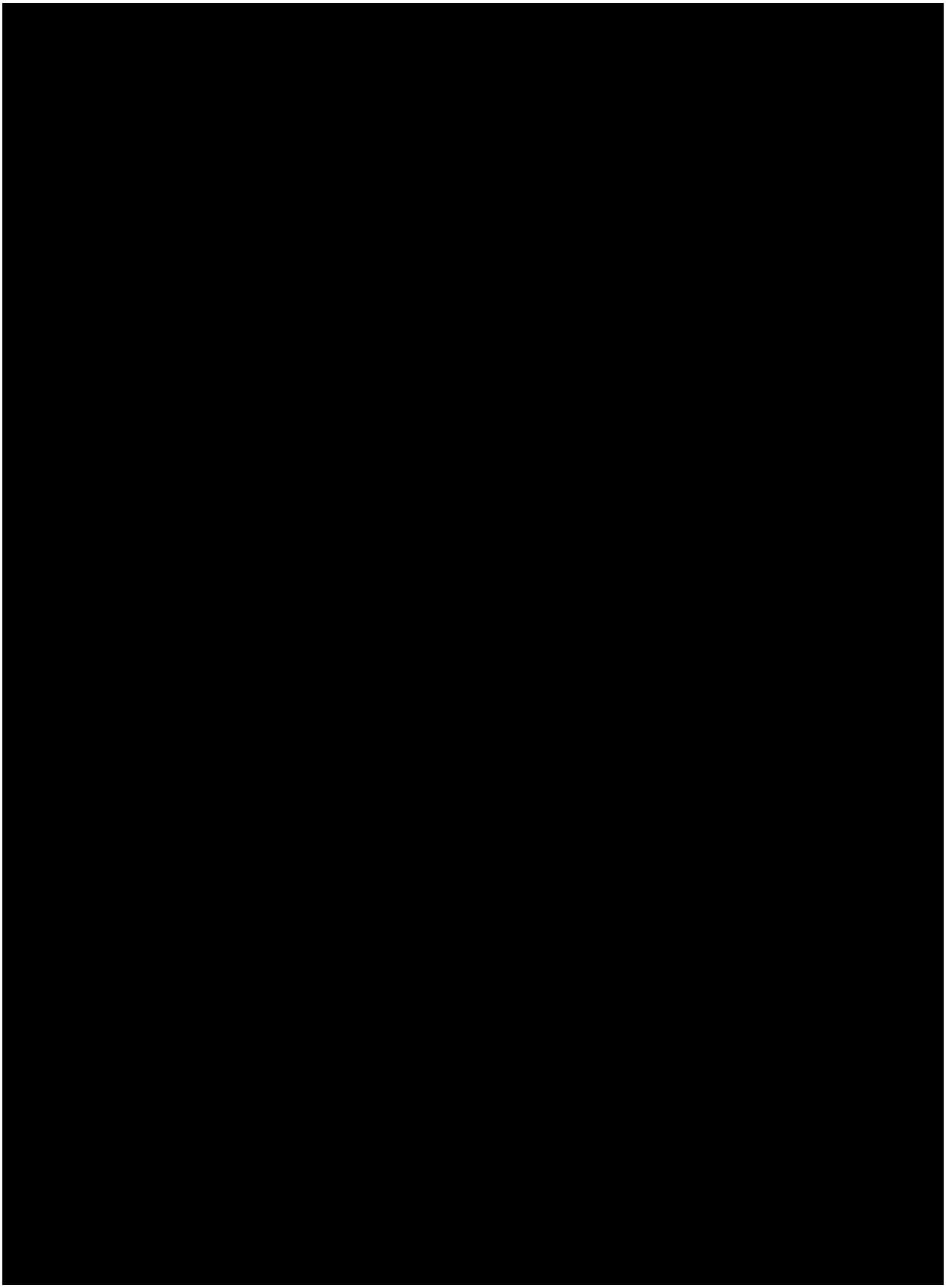
In addition, daily entry starting on the day of the Baseline visit will also include:

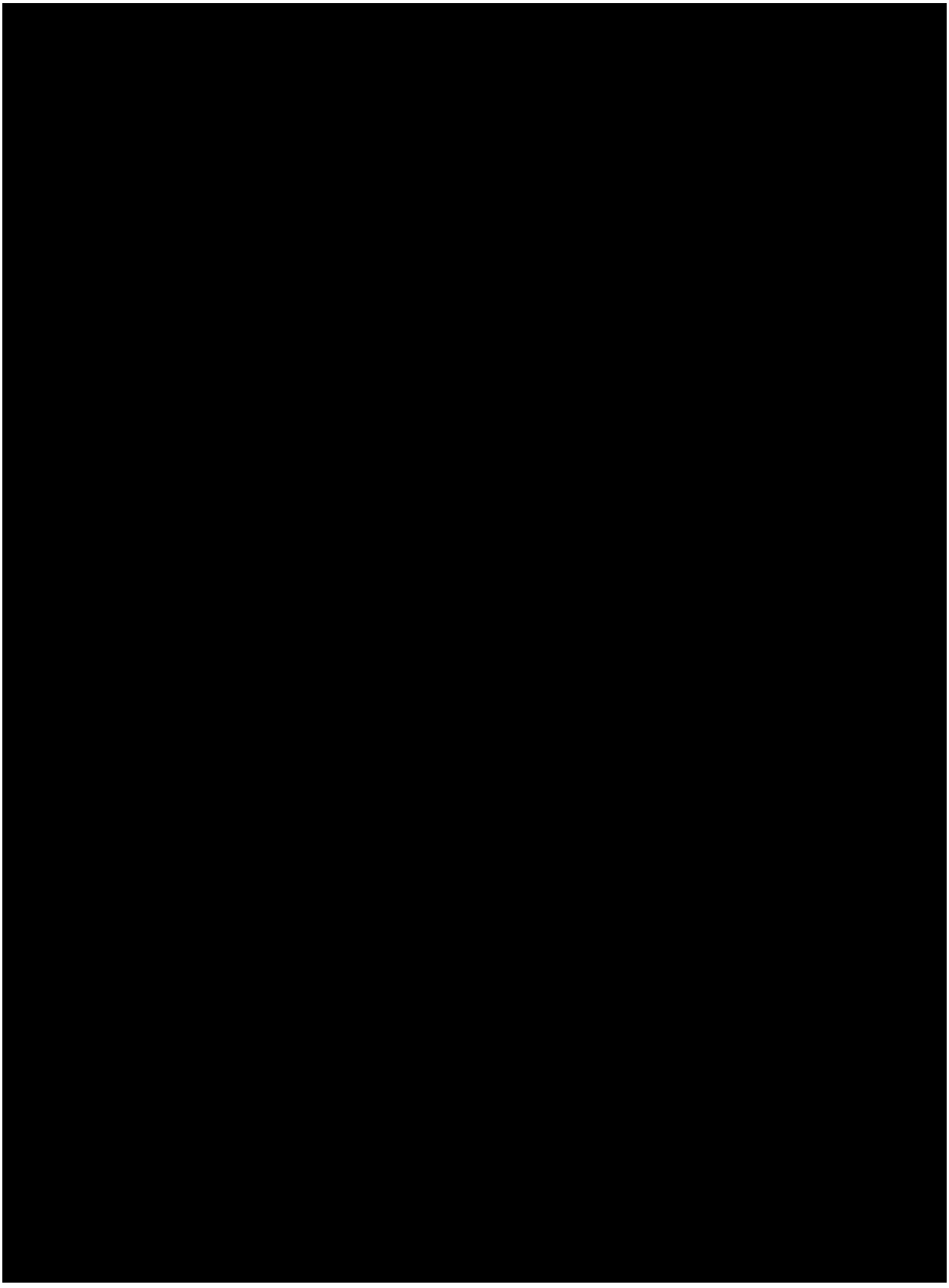
- Intake of study medications (see Section 18)

Rescue medication use, if applicable (see Section 5.5.6) will be entered on the e-diary. Note: rescue therapy can only be used starting at least 4 weeks after Baseline and if found necessary by the Investigator.

6.6.2 Resource utilization

Not applicable.





[redacted]

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign, symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subject with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the appropriate CRF capturing AEs under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade

  mild: usually transient in nature and generally not interfering with normal activities

  moderate: sufficiently discomforting to interfere with normal activities

  severe: prevents normal activities
- its relationship to the study treatment
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding investigational treatment

All adverse events must be treated appropriately. Action taken with investigational treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

The investigator must also instruct each subject to report any new event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing)) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms except non-melonoma skin cancer will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured in the CRF; SAEs also require individual expedited reporting to Novartis Chief Medical Office and Patient Safety as per Section 7.2.2.

7.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to the investigational treatment complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and

reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring should be entered into the appropriate CRFs.

Please refer to Table 14-1 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 14-1 should be followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Table 14-2.

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation

  These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the subject. Repeats of laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the appropriate CRFs.
- If the elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate. Based on the investigator's discretion and/or consultation with Novartis medical monitor, further investigations may be performed.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution
- Complete questionnaire for adjudication as applicable

These investigations can include serology tests, imaging and pathology assessments, and/or hepatologist consultancy, based on the investigator's discretion and/or consultation with

Novartis medical monitor. All follow-up information and the procedures performed must be recorded on the appropriate CRFs.

7.4 Renal safety monitoring

As part of standard renal monitoring, the following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to baseline during normal hydration status
- Urine event:
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 15-1 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

7.5 Cardiac safety monitoring

For ECGs, a notable QTc value is defined as a QTcF (Fridericia) interval of ≥450 msec for males or ≥470 msec for females as well as any increase from Baseline of 30 msec for males and females– all such ECGs will be flagged by the Central CRO and require assessment for clinical relevance and continuance of the subject by the Investigator.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, QTcF >500 msec), a copy of the assessment is sent to the core laboratory for expedited review by the central cardiologist if applicable, and the triplicate ECG is repeated to confirm the diagnosis. Additionally, the following must be done:

- Discontinue study treatment
- Collect a [redacted] sample
- Consult a cardiologist and review electrolytes and concomitant medications
- Perform a follow up ECG 24-48 hours
- Cardiac enzymes or any other cardiac investigation may be done as appropriate

If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Please refer to Appendix 1 for notable vital signs.

7.6 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.7 Pregnancy reporting

When pregnancy occurs in a subject in this study, the study drug must be discontinued, and the subject should stay in the study and follow the assessments. Assessments that are considered as a risk during pregnancy must not be performed. The subject should continue all other protocol assessments. Pregnancy cases have to be unblinded and the treatment communicated to investigator with the request to inform the subject which treatment she was on. This applies also when pregnancy occurs in partners of male subjects.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Post-natal follow up is required until 3 months after the birth.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and

their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis monitoring organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock or when a site is closed, the investigator will receive copies of the subject data for archiving at the investigational site.

The Principal Investigator is responsible for assuring that the data entered by the site personnel into CRF is complete, accurate, and that entry and updates are performed in a timely manner.

8.3 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the

investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples and ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data and Patient Reported Outcomes will be entered into an electronic device by the subject. The device will also be used to capture efficacy assessments entered by the investigator/delegate. The system will be supplied by a vendor(s), who will also manage the database. Exceptionally, if the electronic device is not working, the efficacy assessments and Patient Reported Outcomes may be completed on paper. The data would then be transcribed in the vendor database. The database will be sent electronically to Novartis personnel (or designated CRO).

[redacted] The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using IRT.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

[redacted]

8.4 Data Monitoring Committee

A DMC will review cumulative safety data at scheduled meetings. Of note, the clinical safety plan for this study includes close monitoring by the investigator for signs of abnormal cardiac and hepatic parameters, study entry criteria and treatment discontinuation criteria (Section 5.6).

The collection and summary of these data will be prepared by a designated CRO or Novartis.

Details on the organization and function of the DMC will be described in the DMC charter.

8.5 Adjudication Committee

An adjudication committee will be used to adjudicate rescue therapy and concomitant medication that might have an impact on the primary endpoint. Blinded adjudication of rescue therapy and concomitant medication will be implemented for the final data base lock by considering factors such as the type of medication, indication, timing, frequency and the potential impact of the use. Details regarding the adjudication process will be available in the relevant Adjudication Committee charter.

In addition, an adjudication committee might be used to monitor specific safety events, including, but potentially not limited to, clinically significant cardio- and liver events. The events would be blindly reviewed and adjudicated as they occur during the conduct of a trial. Details regarding the adjudication process would be available, as needed, in the relevant Adjudication Committee charter.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

9.1 Analysis sets

Randomized Set: All subjects randomized are included in the Randomized Set. Subjects will be analyzed according to the treatment assigned to at randomization.

Full Analysis Set (FAS): The FAS comprises all subjects to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization. Mis-randomized subjects (mis-randomized in IRT) will be excluded from FAS. Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject.

Safety Set: The Safety Set includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to treatment received.

9.2 Subject demographics and other baseline characteristics

Analyses will be based on the Randomized Set.

Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

Medical history

Disease-specific medical history and any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary.

9.3 Treatments

Analyses of treatment will be based on the Safety Set.

Study treatment

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain thresholds (e.g., any exposure, ≥1 week, ≥2 weeks, ≥3 weeks, ≥4 weeks, ≥6 weeks, ≥8 weeks, etc.) will be displayed.

Prior and concomitant medication

Prior and concomitant medications will be summarized by treatment separated for AD related and non-AD related medications. AD-related concomitant medications will be summarized by pre-specified categories, route of administration and preferred term. Non-AD related concomitant medications will be summarized by the preferred term.

Rescue therapy (duration of use and amount used) will also be summarized.

9.4 Analysis of the primary variable(s)

All analyses for efficacy data will be based on the FAS.

The primary objective of this study is to characterize the dose response relationship among ZPL389 doses (3, 10, 30 and 50 mg o.d.) and placebo with respect to achievement of IGA response after 16 weeks of treatment, and to select an appropriate dose (or range of doses) to use in Phase 3 studies. The consecutive steps are therefore (1) to confirm an overall dose-response signal, (2) to estimate the minimal ZPL389 dose that shows a relevant effect based on the selected dose response model. The Multiple Comparison Procedures – Modelling (MCP-Mod) methodology (Bretz, et al 2005, Pinheiro, et al 2014, Qualification Opinion on MCP-Mod EMA 2014, FDA endorsement 2015) will be used to address these goals.

9.4.1 Primary Variable(s)

The primary variable for the study is IGA response after 16 weeks of treatment.

IGA response is defined as achievement of an IGA score of 0 or 1 with a 2-point reduction from baseline and no use of confounding therapy as adjudicated up to the assessment time point.

9.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis of a constant dose-response curve for the primary efficacy endpoint will be tested at a significance level of 5% against the one-sided alternative hypothesis of a nonconstant dose response curve using the MCP-Mod methodology.

A logistic regression model will be fitted with response as outcome variable and treatment (dose as categorical variable) and baseline IGA as covariates.

The response Y_{ij} for subject j in dose group i receiving dose d_i is modelled as $Y_{ij} \sim \text{Bin}(1, p_{ij})$ with $p_{ij} = logit^{-1}(\delta_i + \boldsymbol{x}_{ij}'\boldsymbol{\beta})$, $i=1,\ldots, 5, j=1, \ldots, n_i$

where Bin(1,p) denotes the binomial distribution with parameter 1 and p, δ_i is the effect of dose d_i, $\boldsymbol{\beta}$ refers to the vector of regression coefficients corresponding to additional covariates x_{ij} which represent the baseline IGA category. Finally, n_i is the number of subjects allocated to each treatment group. If the covariate baseline IGA prevents fitting of a model, it will be dropped.

Population-average estimates of the logit of the response probability for each dose will be derived based on the results of the logistic regression. This will be a weighted sum of the corresponding estimates for each baseline IGA. The weights will be based on the observed frequencies of the baseline IGA category in the FAS.

The covariance matrix of the estimates will also be estimated based on the logistic regression results. Using the obtained estimates and estimated covariance matrix generalized MCP-Mod (Pinheiro 2014) will be performed.

The following dose-response shapes are selected as candidates:

1. Sigmoid Emax model (with fixed Hill parameter): f(d, θ) = E0+Emax*dh/(dh+ED50h)

- sigEmax1: ED50 = 25 mg, Hill parameter = 4.0
- sigEmax2: ED50 = 30 mg, Hill parameter = 8.0
- sigEmax3: ED50 = 1.85 mg, Hill parameter = 3.0
- sigEmax4: ED50 = 7.5 mg, Hill parameter = 5.0

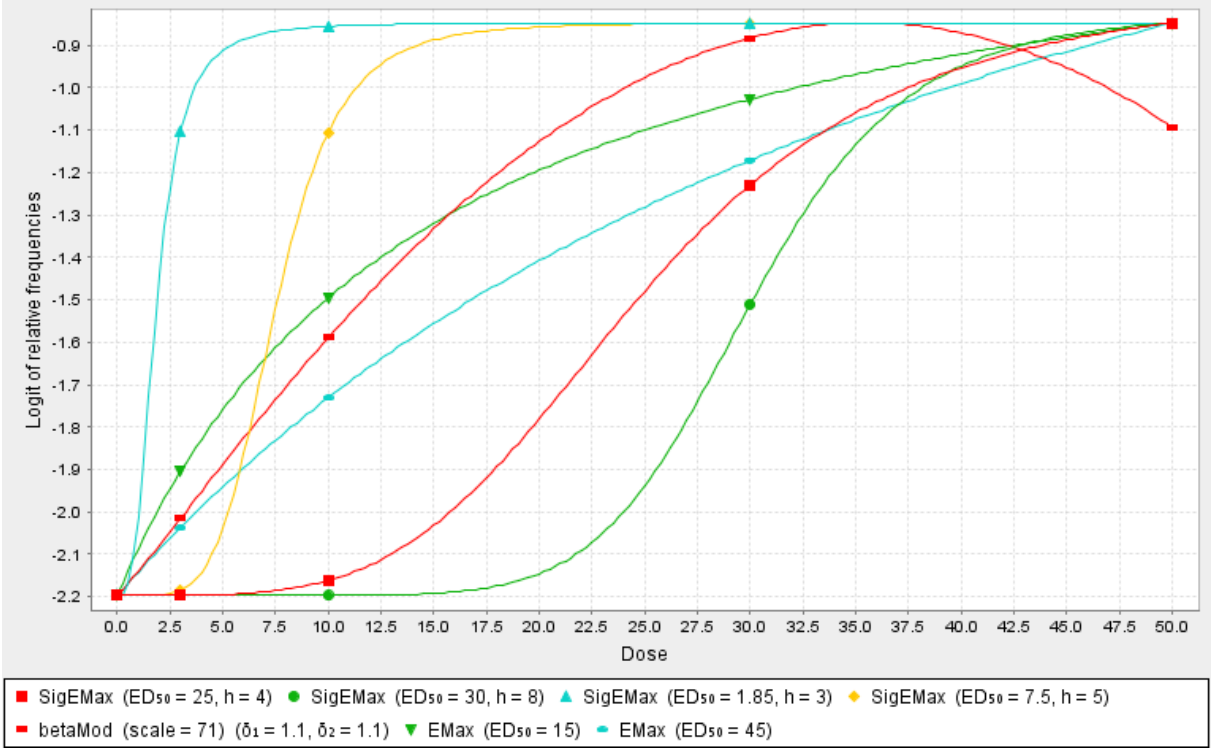
2. Emax model: f(d, θ) = E0+Emax*d/(d+ED50)

- Emax1: ED50 = 15 mg
- Emax2: ED50 = 45 mg

3. beta model: $E0+Emax*B(\delta1, \delta2)*x^{\delta1}(1-x)^{\delta2}$ with x=d/scale

- Scale=71, δ1=1.1, δ2=1.1

Figure 9-1 Candidate models for IGA response at Week 16



For each candidate model a contrast test statistic, based on a linear combination of the treatment estimates per dose will be derived. The contrast coefficients will be chosen to maximize the power to detect the pre-specified candidate models. The global test decision is based on the maximum of the contrast test statistics. A critical value q controlling the type I error rate can be derived from the fact that the contrast test statistics approximately follow a multivariate normal distribution and that their maximum follows the distribution of the maximum of a multivariate normal distribution. If the maximum contrast test statistic exceeds the critical value q, the overall null hypothesis of a constant dose-response curve is rejected and one proceeds to the further estimation steps to determine the dose-response curve and doses achieving target clinical effects using a dose-response model.

Bootstrap model averaging will be used to estimate the dose-response curve, the target dose and to derive confidence intervals. Bootstrap simulation will be performed using the multivariate normal distribution of the estimates of the logit of the response probability for each dose and generalized least-squares fitting of the resulting simulated values (see Pinheiro et al. 2014). The target dose is defined as the dose for which the expected response rate is at least 15% higher than the response rate of placebo which is expected to be about 10%. This will be based on the estimated dose-response curve.

9.4.3 Handling of missing values/censoring/discontinuations

For efficacy variables based on response (e.g. IGA response, EASI50 response, EASI75 response) missing data will be handled as follows:

1. Subjects with use of confounding therapy as adjudicated will be considered as non-responders after application of the therapy.

2. Subjects who discontinue study treatment permanently or discontinue the study due to lack of efficacy or due to adverse event will be considered as non-responder after discontinuation.
3. For subjects who discontinue study or treatment due to other reasons than above or have missing data due to other reasons, missing-at-random will be assumed. The estimates for the logits of the response probabilities as well as the corresponding covariance matrix will be derived applying multiple imputation (MI). The MI model will include IGA categories from all visits from randomization up to Week 16 as well as all EASI score at baseline and absolute change from baseline EASI score for all visits from baseline up to Week 16. For each imputed dataset the logistic regression described in Section 9.4.1 will be performed and results combined for estimation.

For the estimation of the IGA response rates at Week 16 for each treatment group, the estimate for subjects in (3) above will be combined with the non-responders in (1) and (2) above. These combined estimates will be used as input for the MCP-Mod analysis.

If a baseline value is missing, it will be imputed by the mean of the respective treatment group in the respective randomization stratum.

If not stated otherwise, for the secondary [redacted] the observed values will be used for summary statistics, missing values will not be imputed. When doing inference, any missing data will be handled by the respective MMRM model.

For any percent change from baseline analysis, any baseline values equal to zero will be ignored. The total number of zero baseline values will be provided as additional information.

9.4.4 Sensitivity analyses

As a sensitivity analysis, the primary analysis will be repeated on a dataset in which subjects who

- discontinue treatment or study for any reason at any time or
- who take rescue medication at any time

will be considered non-responders.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

All analyses will be based on the FAS if not specified otherwise. For handling of missing data refer to Section 9.4.3.

Percent change from baseline EASI score at Week 16

The null hypothesis of a constant dose-response curve for the EASI score will be tested at a significance level of 5% against the one-sided alternative hypothesis of a non-constant dose response curve using the MCP-Mod methodology (Bretz, et al 2005, Pinheiro, et al 2014, Qualification Opinion on MCP-Mod EMA 2014, FDA endorsement 2015), in analogy to the primary endpoint analysis.

To allow adjustment for correlations between time points within subjects, a mixed effect model for repeated measurements (MMRM) approach is adopted to obtain the least squares means fits.

The mean responses at each individual dose will be obtained through covariate-adjusted treatment effects by modeling the primary efficacy variable using MMRM. The model will contain treatment group, baseline EASI score, geographical region, baseline IGA score, visit, baseline EASI score*visit, and treatment group*visit as covariates, with unstructured covariance matrix.

The covariance matrix of the estimates will also be estimated based on the MMRM results. Using the obtained estimates and estimated covariance matrix generalized MCP-Mod (Pinheiro 2014) will be performed.

The following dose-response shapes are selected as candidates:

1. Sigmoid Emax model (with fixed Hill parameter): f(d, θ) = E0+Emax*d^h/(d^h+ED50^h)

- sigEmax1: ED50 = 25 mg, Hill parameter = 4.0
- sigEmax2: ED50 = 30 mg, Hill parameter = 8.0
- sigEmax3: ED50 = 1.85 mg, Hill parameter = 3.0
- sigEmax3: ED50 = 7.5 mg, Hill parameter = 5.0

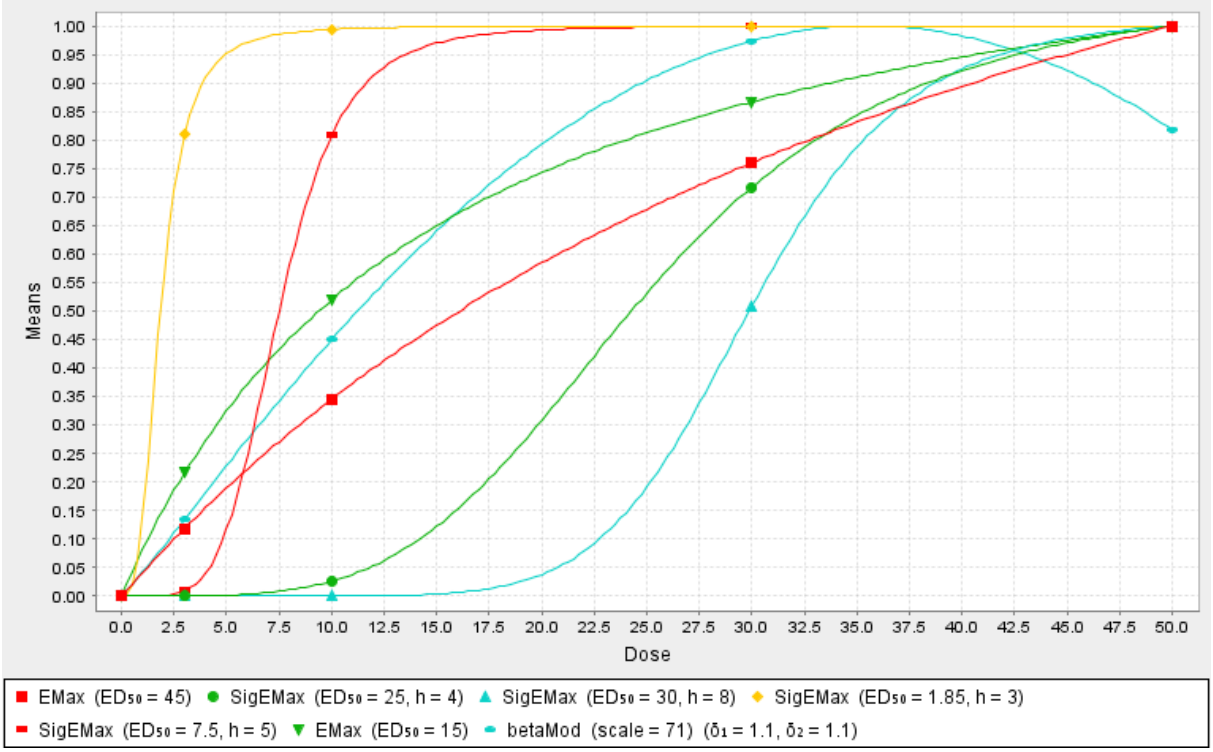
2. Emax model: f(d, θ) = E0+Emax*d/(d+ED50)

- emax1: ED50 = 15 mg
- emax2: ED50 = 45 mg

3. beta model: E0+Emax*B(δ1, δ2)*$x^{\delta 1}(1-x)^{\delta 2}$ with x=d/scale

- beta1: Scale=71, δ1=1.1, δ2=1.1

Figure 9-2 Candidate models for percent change from baseline EASI score at Week 16



For each candidate model a contrast test statistic, based on a linear combination of the treatment estimates per dose will be derived. The contrast coefficients will be chosen to maximize the power to detect the pre-specified candidate models. The global test decision is based on the maximum of the contrast test statistics. A critical value q controlling the type I error rate can be derived from the fact that the contrast test statistics approximately follow a multivariate normal distribution and that their maximum follows the distribution of the maximum of a multivariate normal distribution. If the maximum contrast test statistic exceeds the critical value q, the overall null hypothesis of a constant dose-response curve is rejected and one proceeds to the further estimation steps to determine the dose-response curve and doses achieving target clinical effects using a dose-response model.

Bootstrap model averaging will be used to estimate the dose-response curve and to derive confidence intervals. Bootstrap simulation will be performed using the multivariate normal distribution of the parameter estimates and generalized least-squares fitting of the resulting simulated values.

IGA score

Summary tables will be presented by treatment group and visit which include absolute and relative frequencies. Shifts from baseline IGA score will also be summarized by visit.

IGA/EASI50/EASI75 response

Summary tables will be presented by treatment group and visit which include absolute and relative frequencies. Time courses of the estimated response rate including 95% confidence interval will be plotted for each treatment group. For pairwise comparisons between treatment groups (individual ZPL389 arms versus placebo),

- odds ratios and 95% confidence intervals will be derived using logistic regression with treatment group, baseline IGA and geographical region as covariate
- the individual rate differences of the active treatment groups to placebo and the respective 95% confidence intervals will be derived using a normal approximation.

EASI score as well as absolute and percent change from baseline EASI score

Summary statistics will be presented by treatment group and visit.

To allow for a pairwise comparison between treatment groups, the data will be analyzed using a MMRM with treatment group, baseline EASI, geographical region and baseline IGA, visit, baseline EASI*visit and treatment group*visit as covariate, with unstructured covariance matrix. Time courses of LS means including 95% confidence intervals will be graphically displayed for each treatment group.

BSA will also be summarized analogously to EASI score.

9.5.2 Safety variables

All safety endpoints (i.e. adverse events, laboratory data, vital signs, and ECG) will be summarized by treatment for all subjects of the safety set. All data will be included in the analysis regardless of rescue medication use.

Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term; AEs observed four weeks after last study-drug administration will not be considered as treatment-emergent) will be summarized. AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Serious adverse events will also be summarized.

Separate summaries will be provided for deaths, serious adverse events, and other significant adverse events leading to discontinuation.

Non-treatment emergent adverse events will be reported separately.

Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized. For each parameter, the maximum change from baseline will be analyzed analogously.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

ECG

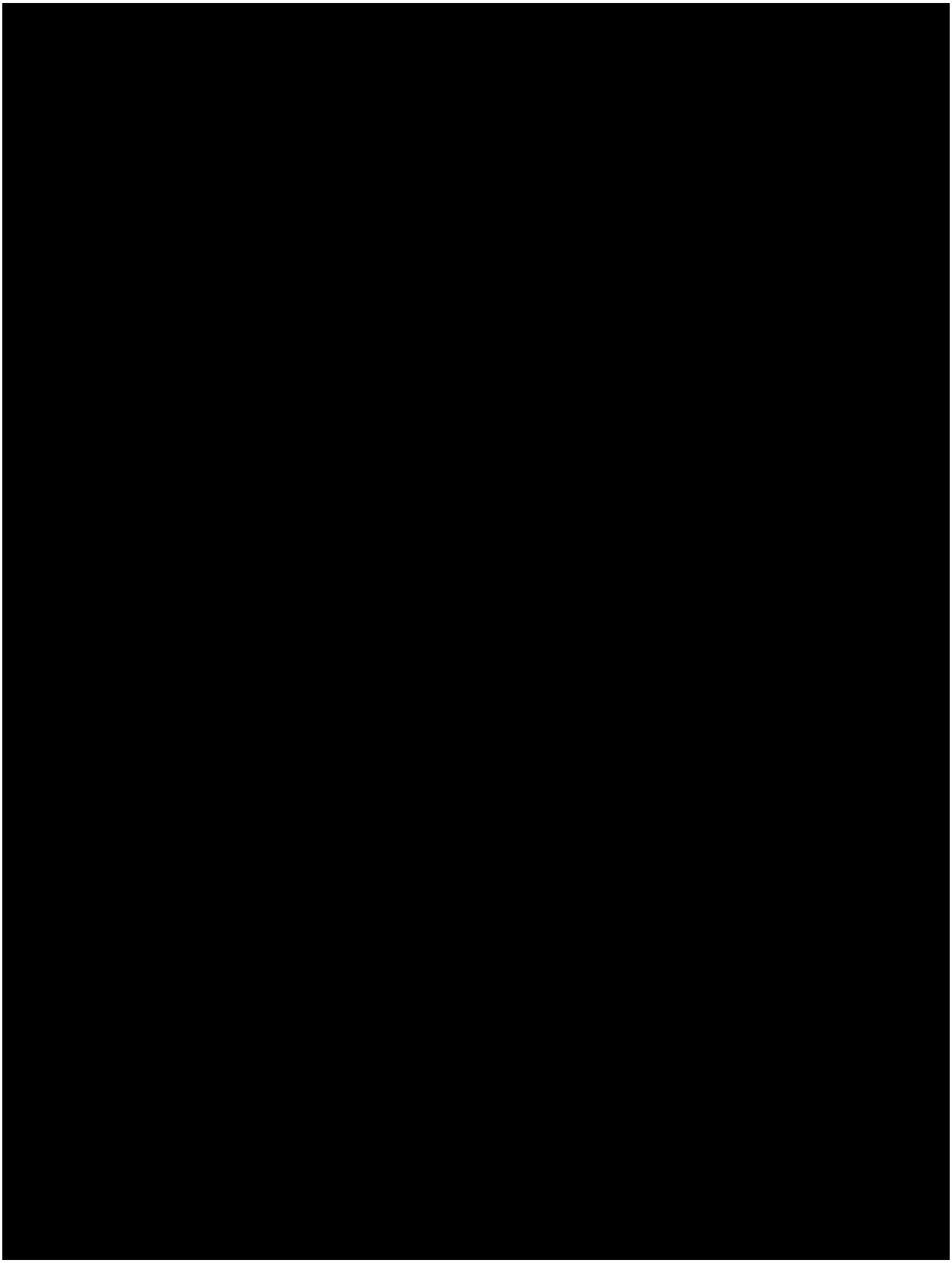
Summary statistics will be provided for ECG parameters. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

9.5.3 Resource utilization

Not applicable.

[redacted]

[redacted]



9.7 Interim analyses

An interim analysis may be performed to support decision making concerning the current clinical study or project. As a consequence the sample size may be reduced, e.g. size of lower dose arms may be reduced by approximately 30%.

9.8 Sample size calculation

The primary objective of this study is to characterize the dose response relationship among ZPL389 doses (3, 10, 30 and 50 mg o.d.) and placebo with respect to achievement of IGA response after 16 weeks of treatment. The sample size was determined with the software ADDPLAN DF, version 3.1.8, with settings for minimum power function and model based contrasts.

The sample size is derived to detect a dose-response with 90% power and a one-sided alpha of 2.5%. Based on literature data Simpson et al 2017, a placebo response rate of 10% is assumed. A maximum treatment effect for ZPL389 of 20%-points higher than placebo is assumed. An

unbalanced allocation ratio of 2:1:1:2:2 corresponding to treatment arms placebo: 3 mg: 10 mg: 30 mg: 50 mg, with more subjects allocated to placebo and the higher doses, is chosen to increase the precision of the estimate for the treatment effect at doses in the expected efficacious dose range.

Under these assumptions, a sample size of 360 subjects in total will be required, randomized to 90:45:45:90:90 subjects corresponding to placebo: 3 mg: 10 mg: 30 mg: 50 mg treatment arms.

In order to show consistency of the treatment effect in Japanese subjects compared to the non-Japanese population, it was estimated that approximately 40 Japanese subjects need to be recruited, i.e. the trial will include approximately 320 non-Japanese subjects and 40 Japanese subjects and the total sample size is 360 subjects.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing signed (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the subject. In cases where the subject's representative gives consent, the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating* the informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they must not be entered in the study.

[redacted]

[redacted]

Declining to participate in [redacted], will in no way affect the subject's ability to participate in the main research study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, documented informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

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13 Appendix 1: Clinically notable laboratory values and vital signs

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Appendix 2 for specific liver event and laboratory test trigger definitions and follow-up requirements.

See Appendix 3 for specific renal alert criteria and actions.

Post-baseline vital signs will be flagged as notable abnormalities as follows:

1. Systolic/Diastolic blood pressure: ≥25% decrease or ≥25 % increase from baseline

2. Pulse: ≥110 bpm with ≥15% change from baseline, or <50 bpm with ≥15% change from baseline

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• ALT >1.5 x ULN and <5 x ULN • AST >1.5 x ULN and <5 x ULN • TBL >1.5 x ULN and <2 x ULN
LIVER EVENTS	• ALT or AST >5 × ULN • ALP >2 × ULN (in the absence of known bone pathology) • TBL >2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST >3 × ULN and INR >1.5 • Potential Hy's Law cases (defined as ALT or AST >3 × ULN and TBL >2 × ULN [mainly conjugated fraction] without notable increase in ALP to >2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST >3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
>8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
>3 × ULN and INR >1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
>5 to ≤8 × ULN	• Repeat LFT within 48 hours (include PT/INR) • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
>3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
>1.5 to ≤5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week (include PT/INR) • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks, if resolved in 4 weeks, no further action
ALP (isolated)		
>2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
>2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
>1.5 to ≤2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Complete CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete CRF	Investigator discretion

[a]Elevated ALT/AST >3 × ULN and TBL >2 × ULN but without notable increase in ALP to >2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥50% compared to Baseline	Follow up within 24-48h if possible Consider study treatment interruption or discontinuation Consider subject hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR) ≥150 mg/g or ≥15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed	
Monitor subject regularly (frequency at investigator's discretion) until either:	
Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or	

Event stabilization: sCr level with ± 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months.

16 Appendix 4: Hepatitis serology criteria

Table 16-1 Hepatitis B serology result, interpretation and subject eligibility

Test	Test result	Interpretation	Subject Eligibility
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible	Subject eligible
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination	Subject eligible unless vaccination performed within three months before baseline
HBsAg Anti-HBc Anti-HBs	Negative Positive Positive	Immune due to natural infection	Not eligible
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acutely infected	Not eligible
HBsAg Anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronically infected	Not eligible
HBsAg Anti-HBc Anti-HBs	Negative Positive Negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection	Not eligible

17 Appendix 5: Investigator Global Assessment (IGA)

The IGA scale used in the study is vIGA-AD™ (Validated Investigator Global Assessment scale for Atopic Dermatitis).

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description

0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

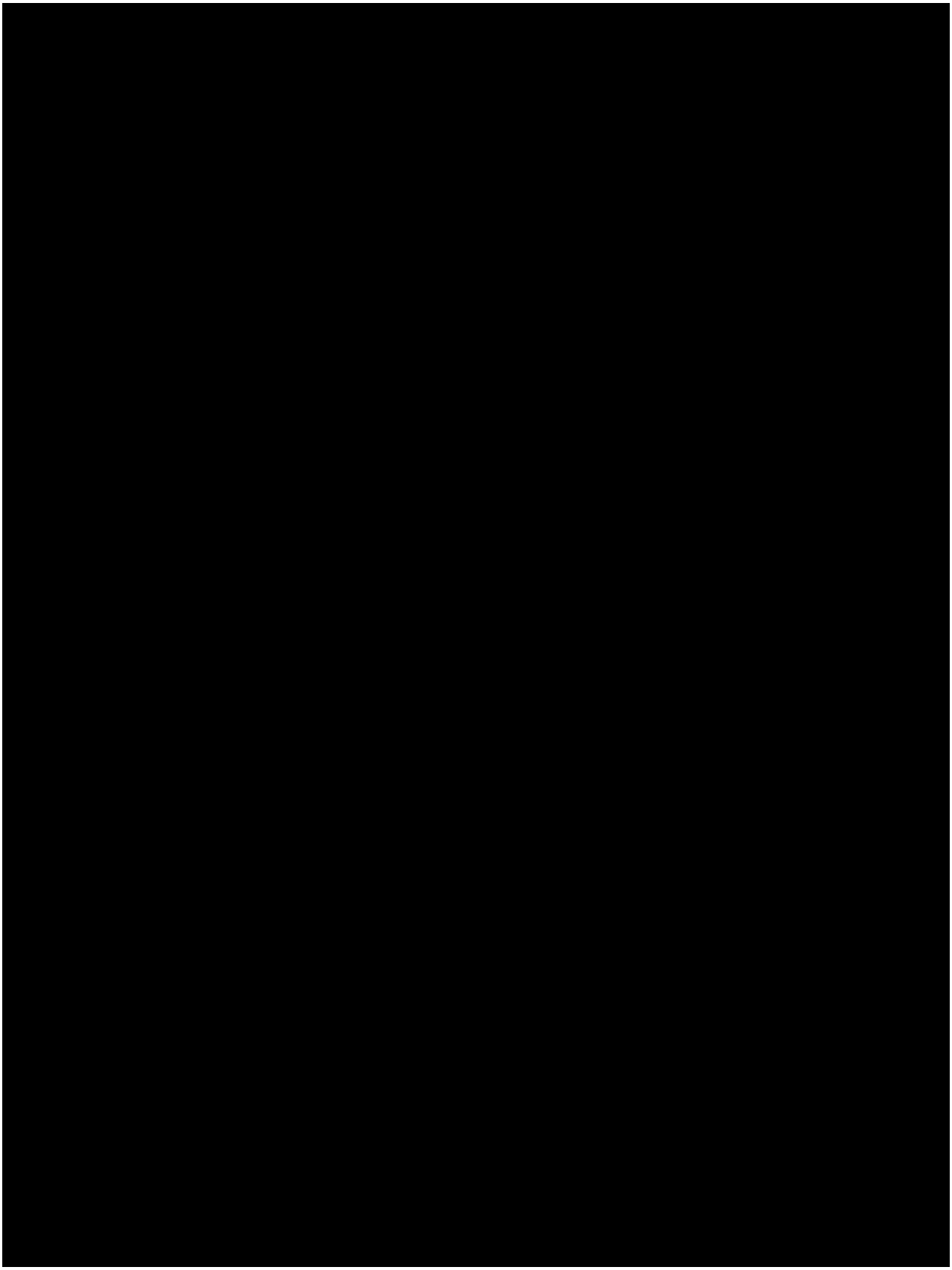
Notes:

- In indeterminate cases, please use extent to differentiate between scores.

  For example: Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".

- Excoriations should not be considered when assessing disease severity.

18 Appendix 6: Patient e-diary



18.3 Tracking study medication intake, emollient and rescue medication

Following the completion of the [redacted], subjects will be asked to answer the following questions every evening:

Did you take your study medications (capsules) today?
☐ No
☐ Yes

Did you apply any emollient today?
☐ No
☐ Yes

Please answer ONLY in case your study doctor has provided you with a rescue cream and asked you to apply it: Did you apply the rescue cream today?
☐ No
☐ Yes

[redacted]