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Novartis Research and Development

ZPL389

Clinical Trial Protocol CZPL389A2203E1 / NCT03948334

A randomized, double blind, multicenter extension to CZPL389A2203 dose-ranging study to assess the short-term and long-term safety and efficacy of oral ZPL389 with concomitant or intermittent use of TCS and/or TCI in adult patients with atopic dermatitis (ZEST Extension)

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List of abbreviations

ACR	albumin-creatinine ratio
AD	Atopic dermatitis
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BSA	Body surface area
CFR	Code of federal regulation
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse event
CYP2D6	Cytochrome P450 2D6
[redacted]	[redacted]
DMC	Data monitoring committee
EASI	Eczema area and severity index
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European medical agency
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H4R	Histamine-4 receptor
HIV	Human immunodeficiency virus
[redacted]	[redacted]
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics Committee
IGA	Investigator's Global Assessment
IL	Interleukin
IMP	Investigational medicinal product
IN	Investigator notification
IRB	Institutional Review Board
IRT	Interactive response technology
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
[redacted]	[redacted]
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

[redacted]	[redacted]
QTcF	Corrected QT interval (by Fredericia's formula)
SAE	Serious adverse event
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reactions
TBL	Total bilirubin
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroid
Th2	T-helper 2 cells
TSLP	Thymic stromal lymphopoietin
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WOCBP	Women of child-bearing potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. topical corticosteroids and/or topical calcineurin inhibitors will be given concomitantly to ZPL389 as a regimen anticipated to be reflective of a real world setting)
Assessment	A procedure used to generate data required by the study
Biological Samples	A biological specimen including, for example, blood (plasma, serum), urine, etc. taken from a study subject.
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.
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 (e.g. rescue medication) up to the assessment time point.
Investigational drug/treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits.
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment but have been inadvertently randomized into the study.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy like rescue TCS).
Patient	An individual with the condition of interest for the study.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
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.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
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 completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A patient participating in this study.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.

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

Protocol summary

Protocol number	CZPL389A2203E1
Full Title	A randomized, double blind, multicenter extension to CZPL389A2203 dose-ranging study to assess the short-term and long-term safety and efficacy of oral ZPL389 with concomitant or intermittent use of TCS and/or TCI in adult patients with atopic dermatitis (ZEST Extension)
Brief title	A study to assess the safety and efficacy of ZPL389 with concomitant or intermittent use of TCS and/or TCI in atopic dermatitis patients.
Sponsor and Clinical Phase	Novartis, Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess short-term and the long-term safety and efficacy of oral ZPL389 (30 mg once daily (o.d.) and 50 mg o.d.) when used concomitantly or intermittently with topical corticosteroid (TCS) and/or topical calcineurin inhibitors (TCI) (according to a standardized regimen, depending on atopic dermatitis lesion severity, in line with common/ real world practice) for up to approximately 2 years in adult patients with atopic dermatitis who previously completed 16 weeks of treatment in the core study (CZPL389A2203).
Primary Objective(s)	To assess the short-term and long-term safety of 30 mg o.d. and 50 mg o.d. ZPL389 with concomitant or intermittent use of TCS and/or TCI up to total of 32 weeks and 116 weeks of treatment.
Secondary Objectives	● To evaluate the efficacy of 30 mg o.d. and 50 mg o.d. ZPL389 with concomitant or intermittent use of TCS and/or TCI as assessed by investigator's global assessment (IGA) response over time. ● To evaluate the efficacy of 30 mg o.d. and 50 mg o.d. ZPL389 with concomitant or intermittent use of TCS and/or TCI as assessed by eczema area and severity index (EASI) over time.
Study design	This 2-year study is a randomized, double blind, parallel group, 2-arm study in up to approximately 270 to 306 subjects with atopic dermatitis (AD) who have completed 16 weeks of treatment in the CZPL389A2203 (core study). In this extension study, subjects who have been receiving ZPL389 30 mg o.d. or 50 mg o.d. doses in the core study, will continue to receive the same doses. Subjects who were receiving ZPL389 3 mg, 10 mg or placebo in the core study will be randomized into 30 mg o.d. or 50 mg o.d. ZPL389 in a 1:1 ratio. All subjects will receive concomitant or intermittent TCS and/or TCI along with ZPL389. Subjects, after completing 100 weeks of treatment during extension study (i.e. up to Week 116 starting from Week 16 of the core study), will enter a treatment-free follow-up period for 4 weeks.
Population	The study population will consist of adult atopic dermatitis patients, female and male, who completed 16 weeks of treatment in the core study (CZPL389A2203). Patients who enter this extension study should be able to use concomitant or intermittent TCS and/or TCI therapy, and comply with inclusion and exclusion criteria for this study.
Key Inclusion criteria	● Signed informed consent must be obtained before any assessment is performed. ● Female and male subjects with atopic dermatitis who have participated in and completed 16 weeks of study treatment in CZPL389A2203 study. ● Willing and able to comply with scheduled visits, treatment plan, laboratory tests, diary completion and other study procedures.

Key Exclusion criteria	● Inability to use TCS and/or TCI concomitantly or intermittently due to history of important side effects of topical medication (e.g. intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or subject's treating physician. ● Subjects who met any study and/or treatment discontinuation criteria during the CZPL389A2203 study. ● 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). ● Subjects taking medications prohibited by the protocol. ● Pregnant or nursing (lactating) women. ● Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they use required methods of contraception during dosing and for 4 weeks after stopping of investigational medication. ● 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.
Study treatment	ZPL389 will be administered orally in capsules in one of the two following treatment arms: ZPL389 30 mg o.d. + TCS and/or TCI ZPL389 50 mg o.d. + TCS and/or TCI
Efficacy assessments	Investigator's global assessment; Eczema Area and Severity Index
Key safety assessments	Adverse event (AE) monitoring, physical examinations including vital signs, monitoring of laboratory markers in blood and urine and electrocardiograms (ECG).
Other assessments	[redacted]
Data analysis	Descriptive statistics will be provided for this study. 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.
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 (Williams et al 1994, Eichenfield 2004). 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 affects 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 (Emerson et al 1998, Hanifin et al 2007).

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 (TCI) 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 patients. Currently the only other systemic therapy approved is dupilumab (anti-Interleukin (IL) 4 Receptor alpha antibody) for treatment moderate to severe AD, but is expected to be reserved for the most recalcitrant patients. 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 a half-minimal (50%) inhibitory concentration (IC) 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.

The chronic and recurrent inflammatory nature of AD requires long-term use of any treatment option; hence, it is essential to investigate long-term safety profile of ZPL389.

1.2 Purpose

The purpose of this study is to assess short-term and long-term safety (frequency of AEs) and efficacy of one of the two doses (30 mg o.d. and 50 mg o.d.) of ZPL389 when used concomitantly or intermittently with topical corticosteroid and/or topical calcineurin inhibitors (according to a standardized regimen in line with common / real world practice that depends on atopic dermatitis lesion severity) for up to approximately 2 years (100 weeks of treatment and 4 weeks of follow-up) in atopic dermatitis adult patients who previously completed treatment in core study (CZPL389A2203).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoints for primary objective**
● To assess the short-term and long-term safety of 30 mg o.d and 50 mg o.d ZPL389 with concomitant or intermittent use of TCS and/or TCI up to total of 32 weeks and 116 weeks of treatment.	● Frequency of AEs at Week 32 (short-term) and Week 116 (long-term).
Secondary objectives	**Endpoints for secondary objectives**
● To evaluate the efficacy of 30 mg o.d and 50 mg o.d ZPL389 with concomitant or intermittent use of TCS and/or TCI as assessed by IGA response over time.	● IGA score over time (absolute and relative frequencies from core study baseline). IGA response is defined as achievement of an IGA score of 0 or 1 with a 2-point reduction from core study baseline without use of confounding therapy (e.g. rescue medication) up to the assessment time point.
● To evaluate the efficacy of 30 mg o.d and 50 mg o.d ZPL389 with concomitant or intermittent use of TCS and/or TCI as assessed by EASI over time.	● EASI score over time (absolute and percent change from core study baseline). EASI-50/EASI-75 response over time: EASI-50/EASI-75 response is defined as achieving ≥ 50%/≥ 75% improvement (reduction) in EASI score compared to baseline without use of confounding therapy (e.g. rescue medication) up to the assessment time point.
[redacted]	

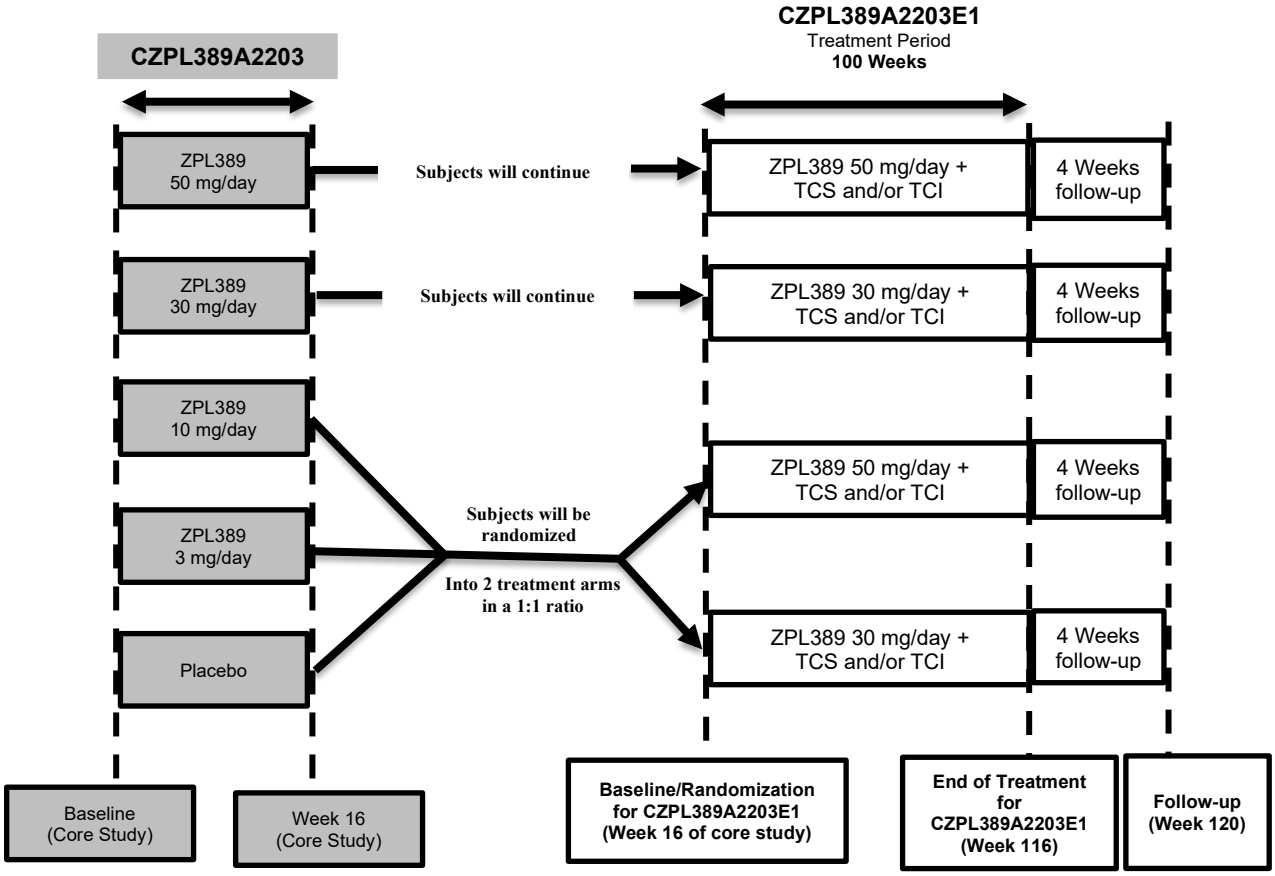
Objectives	Endpoints
[redacted]	

3 Study design

This 2-year study is a randomized, double blind, parallel group, 2-arm study in up to approximately 270 to 306 subjects, considering a projected discontinuation rate of 15% to 25% in the CZPL389A2203 (core study), with AD who have completed 16 weeks of treatment in the core study. In this extension study, subjects who have been receiving ZPL389 30 mg o.d. or 50 mg o.d. doses in the core study, will continue to receive the same doses in double-blinded fashion. Subjects who were receiving ZPL389 3 mg, 10 mg or placebo in the core study, will be randomized into 30 mg o.d. or 50 mg o.d. of ZPL389 in a 1:1 ratio. All subjects will receive concomitant or intermittent TCS and/or TCI along with ZPL389.

After completing 100 weeks of study treatment during extension study (i.e. up to Week 116 including 16 weeks of the core study), subjects will enter the 4 weeks treatment-free follow-up period.

Figure 3-1 Study Design CZPL3892203E1



4 Rationale

4.1 Rationale for study design

This study is planned to collect short-term and long-term safety and efficacy data of ZPL389 by continuing treatment in AD subjects who have completed 16 weeks of treatment in the core study. ZPL389 doses (30 mg o.d. and 50 mg o.d.) selected for the extension phase are anticipated to be most efficacious and tolerable.

The study is a parallel assignment and double blinded to prevent bias in this extension study and to protect the integrity of the core study. Subjects from the core study will roll over into the extension in a manner in which they will not be able to know the dose they received previously in the core study and neither what they receive in this study.

Subjects who previously received either 30 mg or 50 mg ZPL389 in the core study will continue to receive these doses respectively until end of the extension study, this way cumulative data of 30 mg and 50 mg will be generated continuously for a long period. In addition, they will receive standardized TCS/TCI regimen (see Section 4.1.1).

Subject who previously received either 3 mg, 10 mg or placebo for 16 weeks in the core study will be randomized in a 1:1 ratio to receive either 30 mg or 50 mg of ZPL389. Data from these arms will allow confirmation of the added benefit of 30 mg and 50 mg over the lower doses (i.e. 3 mg, 10 mg) or concomitant or intermittent use of TCS/TCI (see Section 4.1.1).

4.1.1 Rationale for choice of background therapy

Topical corticosteroids and/or topical calcineurin inhibitors will be used concomitantly or intermittently to ZPL389 as a regimen anticipated to be reflective of a common / real world clinical practice and depending on the severity of atopic dermatitis lesions.

4.2 Rationale for dose/regimen and duration of treatment

The ZPL389 doses of 30 mg o.d. and 50 mg o.d. were selected as monotonic response is expected for ZPL389 and these are expected to provide better efficacy and will support robust characterization of the long-term safety profile. Additionally, subjects previously receiving lower doses of ZPL389 (3 mg o.d. and 10 mg o.d.) or placebo in the core study will have an opportunity to receive the higher once daily 30 mg and 50 mg doses of ZPL389 in this extension study.

Continuing therapy for two years beyond the core study offers trial participants continued access to a potentially beneficial therapy. Additionally, treatment in this study for approximately 2 years is based on the need for efficacy and safety information during chronic treatment in subjects suffering from AD and for assessing the benefit-to-risk profile of ZPL389 for the long-term management of AD.

Since AD is a systemic inflammatory disease, long-term use of ZPL389 in all patients rolling over to the extension study would allow assessment of the benefit of ZPL389 on one of the most important and prevalent comorbidities of AD which is asthma.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The study does not contain a control drug or combination drug. To support this extension study's purpose and objectives, two doses of ZPL389 will be assigned in parallel and double blinded fashion and this design will offer long-term safety and efficacy characterization of ZPL389 without use of placebo or active control arm. In addition, the use of placebo is not advisable for long-term periods.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned. The primary analysis will be performed after all subjects complete the Week 32 visit. Study modifications are not planned based on this primary analysis. An analysis after all subjects have completed Week 68 visit may be conducted to support drug development decision. A final analysis will be performed after all subjects have completed Week 120 visit (or discontinued prior to Week 120). Investigators, subjects and site personnel will remain blinded until the final database lock has been achieved.

4.5 Risks and benefits

Considering efficacy observed in the Proof of Concept (PoC) study, overall safety observed in studies to date, and the absence of approved oral agent for atopic dermatitis (AD), the benefit/risk of ZPL389 appears to be positive.

In the AD PoC study, subjects receiving a dose of 30 mg o.d. ZPL389 achieved a 50% reduction in EASI score on average over 8 weeks vs. 27% for placebo. Improvements in SCORAD and IGA were observed as well as reductions in body surface area (BSA) affected and lower use of rescue medication in the ZPL389 arm compared to placebo.

In the AD PoC study (N = 98), the safety profile of ZPL389 (30 mg o.d.) was comparable to placebo and the percentages of subjects who reported AEs 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.

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 single ascending dose and multiple ascending dose 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 this study, the single ascending dose part has completed with 49 healthy volunteers exposed to ZPL389 up to doses of 400 mg. All adverse events occurring after intake of ZPL389 were rated as mild and frequencies of AEs were similar between ZPL389 and placebo. The pharmacokinetic (PK) exposure at steady-state of a dose of 50 mg o.d. is expected to be comparable to the PK exposure of a 200 mg single dose. Therefore, multiple doses of up to 50 mg o.d. are considered safe.

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, and no clinically significant changes in ECG parameters including QTc interval prolongation have been observed following single doses of up to 400 mg and multiple doses of up to 50 mg o.d.

Interim analysis data from the ongoing study CZPL389A2101 showed clinically relevant increases of corrected QT interval (by Fredericia's formula) (QTcF) at single doses of 300 and 400 mg ZPL389 (exposures exceeding those expected with 50 mg o.d). 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 effects at a level of regulatory concern (i.e. an upper bound of the 90% confidence interval (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 Drug-Drug Interaction (DDI) simulations, the highest clinically relevant exposure is predicted to occur in a poor metabolizer of Cytochrome P450 2D6 (CYP2D6) treated with a strong inhibitor of CYP1A2. Therefore, in the currently planned extension study, the scenario of highest clinically relevant exposure at a dose of 50 mg o.d. will be prevented by implementing the same measures as in core study:

1. Prohibiting the use of strong CYP1A2 inhibitors for all subjects
2. Prohibiting use of moderate CYP1A2 inhibitors in subjects identified as CYP2D6 poor metabolizers during the core study screening

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.

Long-term toxicity studies have been completed and no further risks have been identified.

In pivotal embryo-fetal development study, there were rare fetal abnormalities and minor maternal toxicity at the highest tested dose, which corresponds to exposure 22 times over the expected exposure in humans with 50 mg once daily (50 mg dose is the highest dose planned in the clinical study). There were no adverse effects in rats, maternal or fetal, at exposures 12 times over the expected exposure in humans with 50 mg once daily. In rabbits, there were no findings. The translatability of the findings in rats to humans is unknown. ZPL389 should not be administered to females of childbearing 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 childbearing potential (WOCBP) will be required to have monthly 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, the benefit/risk appears to be positive.

5 Population

The study population will consist of adult patients with atopic dermatitis, female and male, who have completed 16 weeks of treatment in the core study (CZPL389A2203). They will use concomitant or intermittent TCS and/or TCI therapy, and comply with inclusion and exclusion criteria for this study.

The subject discontinuation rate in the core study is estimated to be 15 % to 25% of all randomized subjects; therefore, approximately 270 to 306 subjects are expected to be part of this extension study.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained before any assessment is performed.
2. Female and male subjects with atopic dermatitis who have participated in and completed 16 weeks of treatment in CZPL389A2203 study.
3. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, diary completion and other study procedures.

5.2 Exclusion criteria

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

1. Inability to use TCS and/or TCI concomitantly or intermittently due to history of important side effects of topical medication (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or subject's treating physician.
2. Subjects who met any study and/or treatment discontinuation criteria during the CZPL389A2203 study (Section 9.1).
3. 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)
4. Subjects taking medications prohibited by the protocol (see Section 6.2.2)
5. Pregnant or nursing (lactating) women
6. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they use 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 (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has 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
    - Use of oral, injected or implanted hormonal methods of contraception, **except in poor CYP2D6 metabolizers**. In the case of this method, **the addition of a male condom is required**
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

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 informed consent form (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 childbearing potential.

7. 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.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

6 Treatment

6.1 Study treatment

Study treatment includes investigational drug (30 mg and 50 mg formulation of ZPL389) which will be provided by Novartis.

6.1.1 Investigational and control drugs

ZPL389 will be administered as powder in capsules and dispensed as 30 mg and 50 mg capsules.

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
ZPL389 30 mg	Capsule	Oral	Blinded	Global
ZPL389 50 mg	Capsule	Oral	Blinded	Global

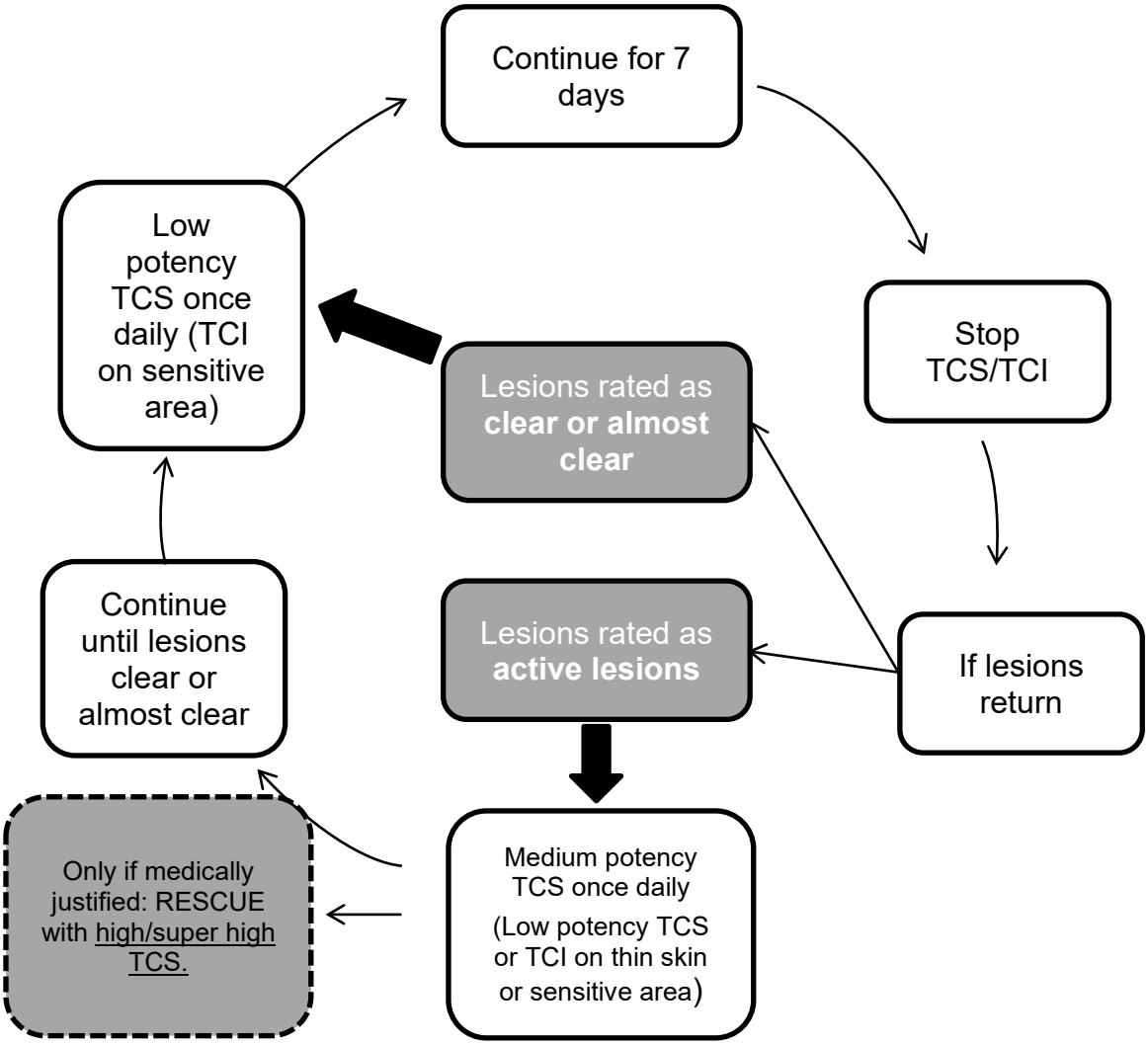
6.1.2 Additional study treatments

TCS/TCI

TCS and/or TCI as available locally will be provided in an open-label type packing.

Starting at **Baseline of extension study,** all subjects will initiate treatment with **TCS** (or TCI in sensitive areas) **using a standardized regimen** and continue the regimen through the end of the study (Figure 6-1).

Figure 6-1 Regimen for TCS/TCI concomitant or intermittent use and rescue TCS



In areas of active lesions:

- Apply **medium potency TCS once daily** to areas with active lesions.
- Low potency TCS or TCI should be used once daily on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) or for areas where continued treatment with medium potency TCS is considered unsafe.

For lesions under control (clear or almost clear):

- After lesions are under control (**clear or almost clear**), initiate or switch to **low potency TCS** (TCI for sensitive area) and treat **once daily for 7 days, then stop.**

If active lesions return, resume treatment with medium potency TCS, with the step-down approach described above upon lesion resolution.

Mometasone furoate 0.1% cream **or Triamcinolone acetonide 0.1% cream** are recommended for medium potency, and **hydrocortisone 1% cream** for low potency.

If use of rescue medication is medically justified, mometasone furoate 0.1% ointment is recommended as a high potency TCS and either betamethasone dipropionate 0.05% ointment or clobetasol propionate 0.05% cream for super high potency TCS. For decision making regarding TCS use, the location of the lesion(s) also needs to be taken into account; please see Section 6.2.3 for details on rescue medication.

Bland emollients:

The use of a bland emollient is required throughout the study and is 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.

6.1.3 Treatment arms/group

Subjects will be assigned, at Baseline of extension study (Week 16 from Baseline of the core study) visit into one of the following 2 treatment arms in a ratio of 1:1:

- ZPL389 30 mg o.d. + TCS and/or TCI
- ZPL389 50 mg o.d. + TCS and/or TCI

TCS and TCI will be sourced locally in each of the participating the countries.

6.1.4 Treatment duration

The planned duration of treatment is approximately 2 years (100 weeks of treatment in extension study), double-blinded treatment period and a 4 weeks treatment-free follow-up period. Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the subject.

6.2 Other treatments

6.2.1 Concomitant therapy

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 on appropriate electronic case report form (eCRF).

Each concomitant drug must be individually assessed against the prohibited medication table (Table 6-2). If in doubt, the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table is NOT allowed during the period specified below in Table 6-2.

Table 6-2 Prohibited medication/therapy

Medication	Prohibition period	Action taken
● Topical treatment for atopic dermatitis such as crisaborole, tar etc., OTHER than those part of the protocol. ● Initiation of treatment of AD with prescription moisturizers or moisturizers containing active ingredients such as ceramides, lactic acid, urea, α-hydroxy- or fruit acids, vitamins A, D or E	a) Treatment period	a) Discontinue prohibited medication and continue study treatment
● 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 ● Oral antihistamines	a) Treatment period	a) 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 the study treatment must be discontinued.
	b) Follow-up period	b) Discontinue prohibited medication unless there is a specific safety risk for the subject, in the opinion of the investigator.
● Phototherapy or tanning booths	a) Treatment period	a) Discontinue prohibited medication/therapy, and continue study treatment
● Any investigational treatment	a) Treatment period	a) Discontinue subject from study treatment
	b) Follow-up period	b) Discontinue prohibited medication
● Any drug known to prolong QTc interval (See https://crediblemeds.org/ for details) ● Drugs known to be hepatotoxic (please see protocol supplementary guidance) ● 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)	a) Within 5 half-lives of Baseline or until pharmacodynamic effect has disappeared, whichever is longer	a) subject is not eligible for this study
	b) Treatment period	b) Discontinue study treatment and enter follow-up
	c) Follow-up period	c) Discontinue prohibited medication

* 2-chlorobenzylidene malononitrile (CS) nasal sprays and eye drops are not considered systemic immunosuppressive treatment.
i.v.: intravenous; i.m.: intramuscular; JAK: Janus kinase.

6.2.3 Rescue medication

Only if medically necessary (i.e. to control intolerable AD symptoms), as assessed by investigator, rescue medication may be provided to study subjects. Rescue treatment in this study is TCS of higher potency than that of previously used when the need for rescue was

determined by the investigator. Subjects should continue treatment with study drug ZPL389. Novartis will provided/reimbursed the rescue medication.

- For lesions persisting or worsening under once daily treatment with medium potency TCS, subjects may be treated (rescued) with high or super-high potency TCS, unless higher potency TCS are considered unsafe.
- The subject is to be monitored for signs of local or systemic TCS toxicity and step-down or stop treatment as necessary.

If use of rescue medication is medically justified, mometasone furoate 0.1% ointment is recommended as a high potency TCS and either betamethasone dipropionate 0.05% ointment or clobetasol propionate 0.05% cream for super-high potency TCS.

Investigator 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 negatively affect the validity of study results. **Use of rescue medication must be stopped as soon as the investigator determines that it is not needed anymore**.

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 (Section 16.6.3). 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. Rescue medication tubes/container will be weighed at the time of dispensing and every subsequent visit and the weight used will be recorded in the appropriate eCRF. Up to Week 32, the subject must also indicate in the patient e-dairy on a daily basis whether the rescue medication was used or not.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Subject numbers will remain the same as in the core study.

The investigator or his/her staff will contact the extension study Interactive Response Technology (IRT) system and provide the requested identifying information for the subject to be registered in the study. The site must select the Electronic Case Report Form (eCRF) book with a matching Subject Number in the electronic data capture (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 eCRF.

6.3.2 Treatment assignment, randomization

At the baseline visit of this extension study (i.e. Week 16 visit of core study), all eligible subjects who have been receiving ZPL389 30 mg o.d. or 50 mg o.d. doses in the core study, will continue to receive the same doses, while the subjects who were receiving ZPL389 3 mg, 10 mg or placebo in the core study, will be re-randomized in a 1:1 ratio via IRT to one of the two treatment arms. The investigator or his/her delegate will contact the extension study 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 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 Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The re-randomization of subjects (who were receiving ZPL389 3 mg, 10 mg or placebo in the core study) will be stratified by previous treatment group in core study and geographical region.

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

6.4 Treatment blinding

Subjects, investigator staff, and persons performing the assessments will remain blind to the identity of the treatment from the time of randomization until final database lock, using the following 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 6.6.2). (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.

Unblinding will only occur in the case of subject emergencies (see Section 6.6.2); at the time of the primary endpoint at Week 32, and final database lock. After all subjects complete Week 32, designated sponsor team members will be unblinded, whereas the subjects, investigator staff, and persons performing the assessments will remain blinded until end of the study to ensure reliable efficacy and safety measures. The randomization codes associated with subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock.

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

For subjects who are unable to tolerate the protocol-specified dosing scheme, dose interruptions of investigational drug are permitted in order to keep the subject on study drug and recorded on the appropriate eCRF. For example, the study medication may be interrupted when the investigator receives an alert for specific parameters and after assessing the subject, is of the opinion that the subject should not be taking the study medication until the issue resolves. Alternatively, the subject may have a planned surgery and may interrupt drug. However when discontinuation criteria are met, the subject must permanently discontinue study medication. The interruptions are only allowed if decided by the investigator to be medically necessary. No down titration or up titration are allowed in this protocol.

6.5.2 Follow-up for toxicities

Please refer to Section 10 for safety monitoring of specific events and required follow-up actions.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Subjects must be instructed to take one capsule per day at the same time every day in the morning (e.g. every day at 8 am). The subject will record the intake of study medication up to Week 32 visit 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 study medication (ZPL389) at home on the day of study visits, but must take it when instructed by study personnel at the investigational site.

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.

6.6.2 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/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

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

Country Organization (CO) (or any entity to which it has delegated responsibility for emergency code breaks) to ensure that un-blinding can be performed at any time.

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

Study treatment must be discontinued after emergency unblinding. However, subjects should continue the study assessments as per protocol.

6.7 Preparation and dispensation

All ZPL389 kits of study treatment assigned by the IRT will be recorded in the IRT system.

Each site will be provided ZPL389 30 mg and 50 mg capsules in packaging of identical appearance.

The ZPL389 study drug packaging has a 2-part label. A unique medication number is printed on each part of this label corresponding to one of the two 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.

TCS and/or TCI will be provided locally by the investigator in an open-label manner to all eligible subjects at each study visit at the time when ZPL389 is also dispensed to the subjects.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

ZPL389:

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 (CPO) 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 during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study 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.

6.7.1.2 Handling of additional treatment

TCS/TCI and emollients:

Use of TCS and/or TCI as concomitant or intermittent therapy, and/or TCS when used as rescue medication (please see Section 6.2.3), subjects must bring all current study medication with them to each site visit.

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording the weight of the TCS/TCI 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 are requested to enter their daily use of emollients in the e-diary up to Week 32 visit, as per assessment schedule (Table 8-1). Above details will be recorded on appropriate eCRF.

6.7.2 Instruction for prescribing and taking study treatment

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

ZPL389 will be provided by Novartis as 30 mg or 50 mg powder in capsules. Bottles of capsules will be dispensed at study visits as per below schedule. All study drugs will be the same color and appearance; they will be supplied in identical bottles, thereby maintaining double-blind conditions.

Study medication will be supplied to the subject as follows:

Table 6-3 Study medication dispensing

Number of bottles	At Each Site Visit on Week						
1 bottle	16	20	24	28			
3 bottles	32	44	56	68	80	92	104

Subjects must be instructed to take one capsule per day at the same time every day 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 up to Week 32 visit. On days of a scheduled study visit, subjects must be instructed to:

- bring all current study medication with them to the visit.
- not to take study medication (ZPL389) at home on the day of study visits, but must take it when instructed by study personnel at the investigational site (just prior to PK sampling and/or after ECG).

7 Informed consent procedures

Eligible subjects may only be included in the study after providing signed (witnessed, where required by law or regulation), Institutional Review Board/Independent ethics Committee (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(s) gives consent (if allowed according to local requirements), 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 agreement by personally signing and dating the informed consent document.

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 Good Clinical Practice (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.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). 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 investigational drug 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 then must be discussed with the subject.

Women of childbearing 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.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

Informed consent must be obtained before conducting any study-specific procedures listed in this protocol.

8 Visit schedule and assessments

The Assessments Schedule (Table 8-1) lists all the assessments and indicates when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1). Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study treatment for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the visit Week 116 will be performed. At this visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the appropriate eCRF. Subjects must return for the follow-up visit Week 120.

Site visits are performed as specified in the assessment schedule (Table 8-1). Subjects must be reminded to be fasting for at least 3 hours before the site visits and to bring their study

medication including any TCS/TCI dispensed previously as well as their e-diaries with them to the site. On days of site visits, subjects should not eat until the ECG is performed.

Table 8-1 Assessment Schedule

Period	Treatment											End of Treatment/TD	Follow-up/TD/PSW	Unplanned
Weeks (starting from baseline of core study)	**16**	**20**	**24**	**28**	**32**	**44**	**56**	**68**	**80**	**92**	**104**	**116**	**120**	**0**
Days	**113**	**141**	**169**	**197**	**225**	**309**	**393**	**477**	**561**	**645**	**729**	**813**	**841**	**-**
Informed consent	X													
Inclusion / Exclusion criteria	X													
Randomization	X													
Physical Examination		S	S	S	S	S	S	S	S	S	S	S	S	S
Electrocardiogram (ECG) [1], Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight					X			X		X		X		
Hematology, Clinical Chemistry, Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Pregnancy Test (serum)								X					X	
Pregnancy Test (urine)	S	S	S	S	S	S	S	S	S	S	S	S		
Adverse Events, Concomitant medications / Surgeries or medical procedures, [redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X
IGA, EASI, [redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
[redacted]														
Patient e-Diary daily entry[2] [redacted]			X											
Patient e-Diary Review	X	X	X	X	X									
[redacted]														
Drug dispensation [4]	X	X	X	X	X	X	X	X	X	X	X			
Dosing at site [5]	X	X	X	X	X	X	X	X	X	X	X	X		
Study Disposition	X													

[1] 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 ECG is done). ECG should be done after 10 min rest in supine position, followed by vital signs while supine and then blood samples.

[2] The investigational site staff must make a phone call to the patient to remind them to switch on the device and start completion of e-Diary. Patient e-Diary will include [redacted] daily use of emollients, study drug, TCS and/or TCI use and rescue therapy (if any).
[redacted]
[4] Subjects should be instructed to take study medication every day at the same time preferably in the morning except on study visit days. Up to week 32 visit, the subject will record the intake of study medication on a daily basis on the subject e-diary.
[5] 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.
Note:

- Patient reported outcomes must be done before physician assessments (IGA, then EASI [redacted]).
- The use of a bland emollient is required throughout the study and is 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.

PWS: Premature Subject Withdrawal; **TD**: Treatment Discontinuation; **X**: Assessment to be recorded in the clinical database or received electronically from a vendor; **S**: Assessment to be recorded in the source documentation only.

8.1 Screening

There is no screening period in this study. All eligible subjects will begin their participation in this study at Week 16 of the core study; making Week 16 of the core study also the baseline visit of this study. At the baseline visit, the investigator will review assessments from Week 0, Week 12 and Week 16 visits of the core study to ensure that eligibility criteria are met.

Subjects who are not able to rollover to the extension study at Week 16 visit, due to delayed start of the study at the site, may still enter the extension study within any time during the 4 weeks follow-up period of the core study. In such cases, the "Follow-up (EOS/PWS)" visit assessments from the core study and baseline assessments required for extension study should be performed.

8.1.1 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, inclusion/exclusion, informed consent, withdrawal of consent (if subject withdrew consent), AE and SAE data collected. AEs that are not SAEs will be followed by the investigator or primary care physician and collected only in the source data.

Subjects who are randomized and fail to start/continue treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data that was collected as a part of the core study will be used for this extension study; therefore this data (except for body weight that need to be collected as specified in the assessment schedule) is not required to be collected again at baseline of this extension study.

8.3 Treatment exposure and compliance

ZPL389:

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 up to Week 32 visit.

Study personnel will review the e-diary entries at each visit up to Week 32 visit, as noted in the assessment schedule (Table 8-1) for study drug intake and discuss with subject any missed doses. Study personnel will also review the amount of study medication returned by the subject at each visit throughout the duration of the study. The total number of doses of study drug intake since the last dispensing visit will be recorded in the appropriate eCRF based on the returned study medication and discussion with the subject.

TCS/TCI:

Subjects must bring the study medication, including emptied tubes/containers of TCS/TCI, to the site at every visit. Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording the weight of the TCS/TCI container(s). 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.

8.4 Efficacy

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. 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 must be performed in an order; IGA then EASI [redacted].

8.4.1 Appropriateness of efficacy assessments

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

8.4.2 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 (Table 8-1). Whenever possible, the IGA assessments should be performed by the same evaluator throughout the study. Please see Section 16.5 for details.

8.4.3 EASI

The EASI (Eczema Area and Severity Index) will be used to make an assessment of the extent and severity of AD (Hanifin et al 2001). The Investigator or trained qualified designee will complete the EASI assessment on each of the visits as outlined in the assessment schedule (Table 8-1). 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 8-2 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 8-3.

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 & neck, 0.3 for trunk, 0.2 for upper limbs and 0.4 for lower limbs).

Table 8-2 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 8-3 EASI score 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% to <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% to <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% to <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% to <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]

8.5 Safety

In addition to the below listed safety assessments, safety monitoring must be done at every visit, as per Section 10, as well as review of concomitant medications with reference to prohibited medications (Table 6-2). The safety assessments and monitoring is in accordance with the risks associated with ZPL389 and/or unknown information.

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 eCRF. Significant findings made after the signing of the informed consent, which meet the definition of an AE, must be recorded on the AE eCRF.

Body Weight:

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.

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.

8.5.1 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.

Clinical Chemistry:

The Chemistry Panel 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 (γGT), 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 Modification of Diet in Renal Disease (MDRD) formula.

If the TBL concentration is increased above 1.5 x upper limit of normal (ULN), direct and indirect reacting bilirubin should be differentiated.

Hematology:

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

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 eCRF. Microscopy must be assessed following an abnormal dipstick test with results captured in the eCRF.

8.5.2 Electrocardiogram (ECG)

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

ECGs must be recorded after at least 3 hours of fasting and after 10 minutes rest in the supine position. The preferred 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 single 12-lead ECGs will be performed as indicated in the assessment schedule.

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 eCRF.

8.5.3 Pregnancy and assessments of fertility

For all WOCBP, pregnancy tests are required at scheduled visits as per Table 8-1. A serum pregnancy test will be performed at Week 68 visit and at the end of the study. Additionally, a urine pregnancy assessment should be done and the result must be evaluated prior to enrollment in to the extension study but only captured on source document.

From Week 32 visit onwards site will dispense pregnancy test kits to the subjects and advice to perform the test at home at an interval of every 4 weeks until next clinic visit.

If a urine pregnancy test is positive, confirmation is required by performing a serum pregnancy testing. In case of urine pregnancy testing conducted at home is positive, the serum sample must be collected at the next site visit. The study treatment must be interrupted unless the serum pregnancy results are available.

When pregnancy occurs in a subject in this study, the study drug must be discontinued, return to the site to perform assessments as per end of treatment Week 116 visit 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.

8.6 Additional assessments

8.6.1 Clinical Outcome Assessments (COAs)

[redacted]. All the patient reported outcomes (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.

8.6.2 Patient e-Diary

Subjects will be asked to complete an e-diary on a daily basis until Week 32. The subject e-diary will be dispensed at baseline visit of the core study to all subjects. The device will remind the subjects to complete the questions. Subjects must bring their e-diaries with them to every scheduled visit. The subject e-diary will be checked by a designated study staff member at each visit; in case of incomplete e-diary entry, the study site staff will counsel the subject on the correct use and frequency of the subject e-diary. Please see Section 16.6 for subject diary questions.

Daily entries will be completed until Week 32 (see Table 8-1)

[redacted]

- Study medication intake
- Emollient use

- TCS and/or TCI and rescue medication

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 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 affect 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 10.1.5)
- Need for continuing prohibited treatment as per Table 6-2.
- 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 Common Terminology Criteria for Adverse Event (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 Appendix 2 and Appendix 3
- Laboratory abnormalities indicating blood and lymphatic system disorders of CTCAE v4.03 of severity grade ≥2 including:
  - Anemia: Hemoglobin <10 g/dL
  - Febrile neutropenia: Absolute Neutrophil Count: (ANC) <1000/mm^3 with a single temperature of >38.3ºC (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 8-1 (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 116 visit) and the Follow-up visit (Week 120 visit), as detailed in Table 8-1, and assessments should be completed and recorded in the appropriate eCRF. The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the appropriate eCRF.

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

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of study 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 should 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. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

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 RoW (Rest of the 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.

9.1.3 Lost 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.

9.1.4 Early study termination by the sponsor

Novartis can terminate the study 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 subjects' welfare and safety.

Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued 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. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g. Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

A subject will be considered to have completed the study when he/she has completed the last visit planned in the protocol (i.e. Week 120 visit).

For all subjects, a safety follow-up visit at Week 120, which is 30 days after the last treatment visit (i.e. Week 116), should be conducted as per assessment schedule (Table 8-1). If the subject is unable to visit the clinic, then at a minimum the information to be collected (e.g. by telephone) at this follow-up visit includes concomitant medications and adverse events.

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 the applicable eCRF.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], 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.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

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 the subject volunteers

them 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 eCRF 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 10.1.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

All adverse events must be treated appropriately. 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
- subject hospitalized/subject's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, 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 (e.g. continuing at the end of the study), 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's Brochure (IB). 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 adverse 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.

10.1.2 Serious adverse events

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
- life-threatening

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).

- 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 to prevent one of the outcomes listed above.

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 be considered as "medically significant" 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 the ICH-E2D Guideline).

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

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 eCRF; SAEs also require individual expedited reporting to Novartis Chief Medical Office and Patient Safety as per Section 10.1.3.

10.1.3 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 treatment visit (i.e. 30 days after Week 116) should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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 *each specific component of study 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.

10.1.4 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.

10.1.5 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 dose administration record (DAR) eCRF 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 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (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

10.2 Additional Safety Monitoring

10.2.1 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 eCRFs.

Please refer to Table 16-1 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site as summarized below. Detailed information is outlined in Table 16-2.

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 eCRFs.

- 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.

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 eCRFs.

10.2.2 Renal safety 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 16-3 in Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

10.2.3 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 – all such ECGs will be flagged by the Central contract research organization (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, conduction abnormality of QTcF >500 ms), 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 PK 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 immediately (for example cardioversion).

Please refer to Appendix 1 for notable vital signs.

10.2.4 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site

investigators participating in the study. The DMC will review safety data at defined intervals and recommend to the sponsor whether to continue, modify or terminate the study. 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 9).

A designated CRO or Novartis will prepare the collection and summary of these data.

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

10.2.5 Adjudication committee

An adjudication committee may be used to monitor specific safety events, including, but potentially not limited to, clinically significant cardio and liver events and ensure that all treatment outcomes are judged uniformly, using standard criteria and processes. The events will be blindly reviewed and adjudicated as they occur during the study conduct.

Details regarding the adjudication process will be available, in the relevant Adjudication Committee charter.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff. The investigator/designee is responsible for assuring that all the data (recorded or entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered into the eCRFs 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 to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the World Health Organization (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). The subject will enter diary data and Patient Reported Outcomes into an electronic device. The device will also be used to capture efficacy assessments entered by the investigator/delegate. A vendor, who will also manage the database, will supply the system. 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 the vendor database.

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 an Interactive Response Technology (IRT). A vendor, who will also manage the database, will supply the system. The database will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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 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.

11.3 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 (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and 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 Good Clinical Practice, 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. 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, ECG, and the results of any other tests or assessments. All information on eCRFs 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 eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data after all subjects completed the Week 32 visit and at the time of the study 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, the data will be analyzed by treatment groups and p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

12.1 Analysis sets

Randomized Analysis Set (RAS): All subjects randomized are included in the RAS. 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 by randomization. Following the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure. Mis-randomized subjects (mis-randomized in IRT) will be excluded. 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 (SAF): The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to treatment received.

12.2 Subject demographics and other baseline characteristics

Analyses will be based on the Randomized Analysis Set.

Demographics and baseline characteristics:

Summary statistics will be presented for continuous demographic and baseline characteristic variables from core study 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 core baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary.

12.3 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.

TCS/TCI therapy use, duration of use, amount used, proportion of days without TCS/TCI use, and potency category (high/medium/low) will be summarized.

12.4 Analysis of the primary endpoint

The primary objective for this study is to analyze the adverse event (AE). All analyses for adverse events will be based on the SAF.

12.4.1 Definition of primary endpoint

The primary variable is frequency of AE. Please refer to Section 12.5.2 for detailed analyses.

12.4.2 Statistical model, hypothesis, and method of analysis

Only descriptive statistics will be provided, no inferential statistics will be conducted.

12.4.3 Handling of missing values/censoring/discontinuations

For efficacy, variables based on response (e.g. IGA response, EASI-50 response, EASI-75 response) missing data will be handled as follows:

1. Subjects with use of confounding therapy (e.g. rescue medication) based on Anatomical Therapeutic Chemical (ATC) codes and/or timing of dosing 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 as well as all EASI score at baseline and absolute change from baseline EASI score for all visits. For each imputed dataset, the logistic regression will be performed and results combined for estimation.

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 other secondary [redacted] the observed values will be used for summary statistics, missing values will not be imputed.

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.

12.4.4 Sensitivity and Supportive analyses

Not applicable.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint

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

IGA/EASI-50/EASI-75 response:

IGA response: subjects achieving an IGA score of 0 or 1 with a 2-point reduction from core study baseline without use of confounding therapy; e.g. rescue medication, up to the assessment time point.

EASI-50 response: subjects achieving ≥ 50% improvement (reduction) in EASI score compared to baseline (without use of confounding therapy; e.g. rescue medication, up to the assessment time point) are defined as EASI-50 responders.

EASI-75 response: subjects achieving ≥ 75% improvement (reduction) in EASI score compared to baseline (without use of confounding therapy; e.g. rescue medication, up to the assessment time point) are defined as EASI-75 responders.

Summary tables for the responses 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.

Heat map will be provided based on EASI response (no EASI-50 response; EASI-50 response, but not EASI-75 response, EASI-75 response, but not EASI-90 response; EASI-90 response).

IGA score:

Summary tables will be presented by treatment group and visit, which include absolute and relative frequencies. Heat map will be provided for IGA score over time.

EASI score:

Summary tables will be presented by treatment group and visit for EASI score, absolute change and percent change from baseline on EASI score.

12.5.2 Safety endpoints

All safety endpoints (i.e. adverse event, laboratory data, vital signs, and ECG) will be summarized by treatment for all subjects of the safety set.

Adverse events:

Treatment emergent adverse events will be summarized. Only primary paths within MedDRA will be considered for adverse event reporting. The definition for "treatment emergent" is as follows:

- Events started on or 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

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.

All adverse event including non-treatment emergent adverse events will be listed.

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 laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values. For each parameter, the maximum change from baseline will be analyzed analogously. Number and percentage of subjects with notable abnormalities will be summarized.

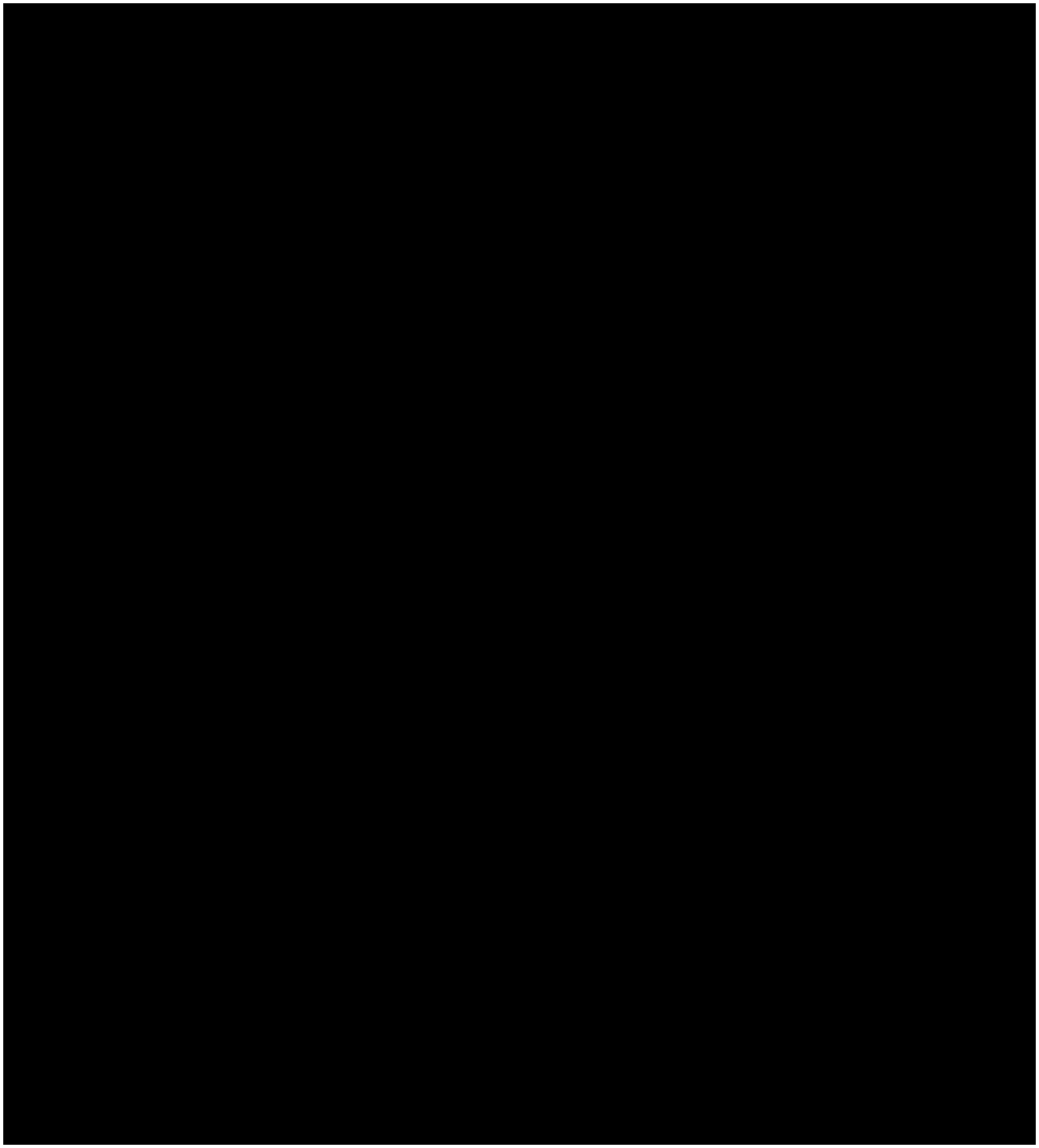
Vital signs:

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. Number and percentage of subjects with notable abnormalities will also be summarized.

ECG:

Summary statistics will be provided for ECG parameters. Number and percentage of subjects with notable abnormalities will be summarized.



12.7 Interim analyses

No formal interim analysis is planned. The primary analysis will be performed after all subjects have completed Week 32 visit. An analysis after all subjects have completed Week 68 visit may be conducted as well. A final analysis will be performed after all subjects have completed Week 120 visit (or discontinued prior to Week 120).

12.8 Sample size calculation

Assuming the discontinuation rates of 5%, 10%, 20%, and 30% in core study, the sample size in each treatment group (ZPL389 50 mg + TCS/TCI, ZPL389 30 mg + TCS/TCI) will be 171, 162, 144 and 126, respectively in extension study. The approximate subject numbers based on different discontinuation rates in core study are listed as below.

Table 12-1 Sample size in the study

Subject number in core study	Discontinuation rate	subject number in extension study	Subject number in each treatment group in extension study
360	5%	342	171
360	10%	324	162
360	20%	288	144
360	30%	252	126

With a sample size in the extension study receiving ZPL389, the chances for an AE with an underlying occurrence rate of 1%, 2.5%, 5%, 10% to be observed at least once for the given doses (ZPL389 50 mg + TCS/TCI or ZPL389 30 mg + TCS/TCI) are very high and >71% for all cases, which is shown in Table 12-2.

Table 12-2 The chances to detect at least one AE in this study

Subject number in each treatment group	AE occurrence rate	Power to detect at least one AE
171	1%	82.1%
	2.5%	98.7%
	5%	99.9%
	10%	100%
162	1%	80.3%
	2.5%	98.3%
	5%	99.9%
	10%	100%
144	1%	76.5%
	2.5%	97.4%
	5%	99.9%
	10%	100%
126	1%	71.8%
	2.5%	95.9%
	5%	99.8%
	10%	99.9%

13 Ethical considerations and administrative procedures

13.1 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.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (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.

13.3 Publication of study protocol and results

The key design elements of this protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. 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 such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) 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 SOPs, and are performed according to written Novartis processes.

14 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.

14.1 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 required for subject safety 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, Novartis should

be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 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

16.2 Appendix 2: Liver Event and Laboratory Trigger Definitions and Follow-up Requirements

Table 16-1 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 16-2 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 eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
ALT or AST		
>8 × ULN	● Discontinue the study treatment immediately ● Hospitalize if clinically appropriate ● Establish causality ● Complete eCRF	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 eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, and γGT until resolution[c] (frequency at investigator discretion)
>5 to ≤8 × ULN	● Repeat LFT within 48 hours ● If elevation persists, continue follow-up monitoring ● If elevation persists for more than 2 weeks, discontinue the study drug ● Establish causality ● Complete eCRF	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 eCRF	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 ● 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 eCRF	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 eCRF	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 eCRF	ALT, AST, TBL, Alb, PT/INR, ALP, and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Complete eCRF	Investigator discretion

Criteria	Actions required	Follow-up monitoring
[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; Alb: Albumin; PT; prothrombin time; INR: international normalized ratio.		

Based on investigator's discretion, investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions

Table 16-3 Specific Renal Alert Criteria and Actions

Serum Event	Actions
Serum creatinine (sCR) increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48 h 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 eCRF: 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.	

16.4 Appendix 4: Hepatitis Serology Criteria

Table 16-4 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

Anti-HBc: Anti-Hepatitis B core antigen antibody; Anti-HBs: Anti-Hepatitis B surface antigen antibody; HbsAg: hepatitis B virus surface antigen; IgM: Immunoglobulin M

16.5 Appendix 5: Investigator Global Assessment (IGA)

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

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.

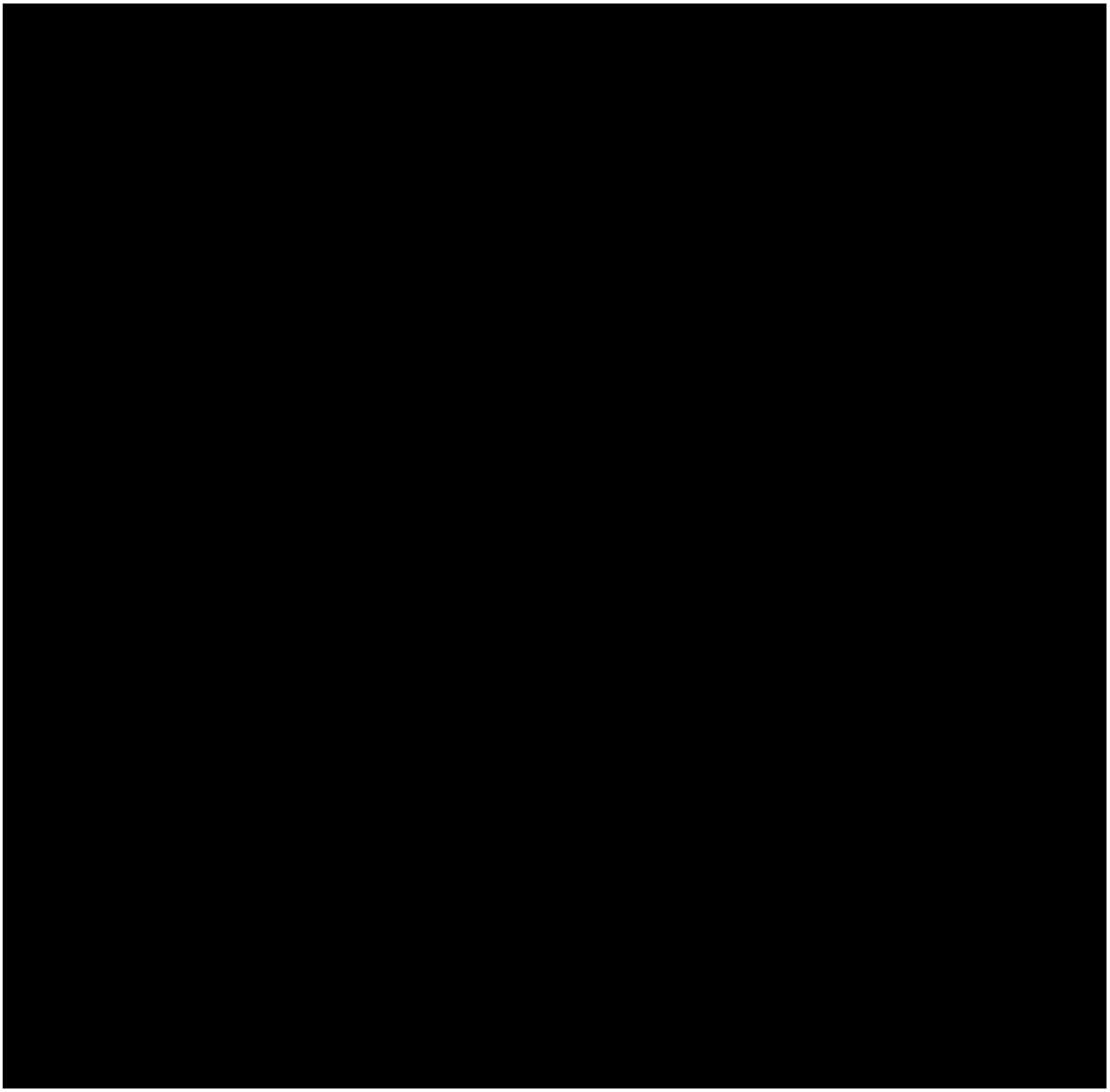
Notes:

- 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.

16.6 Appendix 6: Subject e-diary



[redacted]

16.6.3 Tracking study medication intake, emollient, TCS and/or TCI and rescue medication

Following the completion of the Eczema Symptom and Impact questions shown above, 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

Did you apply Topical Study Treatment (provided by your study doctor) 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