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CMK389

Clinical Trial Protocol CCMK389B12201 / NCT04836858

A randomized, subject and investigator blinded, placebo-controlled multicenter study to assess the efficacy and safety of CMK389 in patients with moderate to severe atopic dermatitis

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List of abbreviations

AD	Atopic Dermatitis
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AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
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BMI	Body Mass Index
BSA	Body-surface area
BUN	Blood Urea Nitrogen
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
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DMC	Data Monitoring Committee
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EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
EOT	End of Treatment
FIH	First in Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GWAS	Genome-wide association studies
h	Hour
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus

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i.v.	intravenous
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFNγ	Interferon gamma

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IGA	Investigator Global Assessment
IL-18	Interleukin-18
IL-18BP	Interleukin-18 Binding Protein
IL-18R1	Interleukin-18 receptor 1
IL4Ra	Interleukin 4 Receptor alpha
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAK	Janus Kinase
K14	Keratin 14
LDH	lactate dehydrogenase

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LTBI	Latent tuberculosis (TB) infection
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MoA	Mechanism of Action
NIRT	Novartis Interactive Response Technology
NK	Natural killer cells
NLR	NOD-like receptor
NLRC4	NLR family CARD domain containing 4
NLRP3	NLR family pyrin domain containing 3
NRS	Numerical Rating Scale
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
PDE4	Phophodiesterase 4

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pQTL	protein quantitative trait loci
PRO	Patient Reported Outcomes
QD	Once a day
QMS	Quality Management System

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QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RBC	red blood cell(s)
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SEB	Staphylococcal enterotoxin B
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCI	Topical calcineurin inhibitors
TCS	Topical Corticosteroids
TDAR	T-cell dependent antibody response
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WoCBP	Women of child-bearing potential
XIAP	X-linked inhibitor of apoptosis protein

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. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
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
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
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 participants	Mis-randomized participants 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)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
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	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or 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 participant
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
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
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.

Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol summary

Protocol number	CMK389B12201
Full Title	A randomized, subject and investigator blinded, placebo-controlled multicenter study to assess the efficacy and safety of CMK389 in patients with moderate to severe atopic dermatitis (AD)
Brief title	Study of efficacy and safety of CMK389 in moderate to severe AD participants
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Biologic
Study type	Interventional
Purpose and rationale	The main aim of this study is to assess preliminary efficacy, safety and tolerability of CMK389 in participants with moderate to severe AD
Primary Objective(s)	To assess the efficacy of CMK389 versus placebo in participants with moderate to severe AD
Secondary Objectives	To assess the safety and tolerability of CMK389 in participants with moderate to severe AD
Study design	This is a randomized, placebo-controlled, parallel-group, non-confirmatory, investigator and participant blinded study in adult participants with moderate to severe AD. Commercially Confidential Information During CCI of treatment period CMK389 or placebo will be administered intravenously (i.v.) or subcutaneously (s.c.) Commercially Confidential Information Approximately 64 eligible participants with AD will be randomized into one of four treatment arms (randomization 4:1:2:1): • Arm 1: 32 participants treated i.v. with 10 mg/kg CMK389 • Arm 2: 8 participants treated i.v. with placebo • Arm 3: 16 participants treated s.c. with 300 mg CMK389 • Arm 4: 8 participants treated s.c. with placebo
Study population	The study population will consist of adult female and male participants with moderate to severe AD.

Key Inclusion criteria	• Adult male or female participants with chronic AD, according to the American Academy of Dermatology Consensus Criteria (Eichenfield et al 2014), aged 18 to 65 years, present for at least 1 year before screening.
	• Moderate to severe AD defined as:
	  • Investigator Global Assessment (IGA) score of ≥ 3 (on a scale of 0 to 4, in which 3 is moderate and 4 is severe) at Baseline (or Screening if Baseline is omitted)
	  • Eczema Area and Severity Index (EASI) score of ≥ 12 at Baseline (or Screening if Baseline is omitted)
	  • Pruritus Numerical Rating Scale (NRS) of at least ≥ 3 at Baseline (or Screening if Baseline is omitted)
	• Participants who are candidates for a systemic therapy, defined as e.g. inadequate response to treatment with topical medications, or from whom topical treatments are otherwise medically inadvisable (e.g., because of important side effects or safety risks, patients with large affected body surface areas), as assessed by the investigator
	• Participants must have a body mass index (BMI) at screening within the range of 18 to ≤35 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2

Key Exclusion criteria	• Any skin disease that, in the opinion of the investigator, would confound the diagnosis or evaluation of AD disease activity (e.g., Netherton Syndrome, or other ichthyoses, cutaneous T-Cell Lymphoma, extensive contact dermatitis, chronic actinic dermatitis and other forms of eczema, such as seborrheic and microbial eczema).
	• Participants taking prohibited medication not completing the wash out period as specified in Table 6-2.
	• Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
	• Any active, recent or recurrent systemic or localized infection at screening or prior to first treatment which in the opinion of the investigator immunocompromises the participant and/or places the participant at unacceptable risk for immunomodulatory therapy, such as:
	  • Any acute bacterial, fungal, or viral (e.g. herpes simplex, herpes zoster, chicken pox) skin/mucosal infection that has not resolved within 2 weeks prior to first treatment or within 12 months in case of ezcema herpeticum
	  • Clinically infected AD within 4 weeks prior to first treatment.
	  • Tuberculosis (TB)
	  Human Immunodeficiency Virus (HIV)
	  Hepatitis B
	  Hepatitis C
	  • Evidence of active or latent tuberculosis (TB) infection, as determined by Quantiferon test at screening (Note: if Quantiferon test is indeterminate, it may be repeated once. Two indeterminate Quantiferon tests will be considered as evidence of TB infection. Furthermore, after anti-TB treatment, participants with history of or latent TB may become eligible according to national guidelines)
	  • History of primary or secondary immunodeficiency, or a positive HIV (Chemiluminescence and Polymerase Chain Reaction)) test result

	• Positive hepatitis B surface antigen (HBsAg) and/or positive hepatitis B core antibody (anti-HBc) • Positive hepatitis C antibody (anti-HCV), unless it can be documented that the participant has received highly-effective HCV-specific antiviral therapy, HCV RNA levels are measured, and HCV RNA is undetectable at least 12 weeks after conclusion of HCV-specific antiviral therapy • Any other current or past clinical significant medical condition, including psychiatric condition, which in the Investigator's opinion may interfere with safety of participants, study objectives or adherence to the protocol. • Participants with confirmed abnormal absolute neutrophil count (ANC) of <1.5 x 10^9/L or with thrombocytopenia of < 75.0 x 10^9/L at screening and baseline (unless baseline visit is omitted) • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases • History of hypersensitivity to any component of the study drug product, or to drugs of similar chemical classes (i.e., IgG-1 related biologic agents) • History of severe or serious allergy or hypersensitivity reactions, such as anaphylactic shock, asthma, or uncontrolled urticaria. • Women of child-bearing potential (WoCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 6 months after last dose.
Study treatment	• CMK389 10 mg/kg i.v.: CCI • Matching placebo i.v.: CCI • CMK389 300 mg s.c: CCI • Matching placebo s.c.: CCI
Treatment of interest	The randomized treatment (the investigational treatment CMK389 or the placebo treatment) taken for the entire study duration without any use of prohibited medications or use of rescue medication taken after the first 6 weeks
Efficacy assessments	IGA response (defined as clear or almost clear and at least 2 point reduction from baseline) at Week 16
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Key safety assessments	• AE monitoring using CTCAE grading • Physical examinations • Monitoring of laboratory markers in blood and urine • ECG • Vital signs

Other assessments	Commercially Confidential Information
Data analysis	The IGA data will be listed and summarized by treatment group. Placebo groups will be pooled. Commercially Confidential Information All information obtained on adverse events will be displayed by treatment group (CMK389 10 mg/kg i.v., Placebo i.v., CMK389 300 mg s.c., Placebo s.c., and Pooled placebo) and participant. The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized.
Key words	Atopic Dermatitis, Safety, Efficacy

1 Introduction

1.1 Background

Atopic dermatitis (AD) is a chronic inflammatory skin disease that commonly presents first during early infancy and childhood. It is characterized by poorly defined erythema with edema, vesiculation, and weeping in the acute stage and skin thickening (lichenification) in the chronic stage (Eichenfield 2004, Williams et al 1994). These symptoms result in a severely reduced quality of life (QOL). In particular, pruritus (or itch), that continues throughout the day and worsens at night causes sleep loss and impacts everyday activities and psychosocial wellbeing (Bieber 2010, Weidinger and Novak 2016). AD is commonly associated with other atopic and inflammatory disorders, such as asthma, allergic rhinitis and food allergy. Usually the disease regresses during adolescence but symptoms may also persist into adulthood. Two to ten percent of adults and up to 20% of children have AD, of which approximately 70% and 16%, respectively, are moderate to severe (Hanifin and Reed 2007, Emerson et al 1998). Depending on the severity of the disease different therapeutic options may be proposed. The basis of AD treatment are emollients in patients of all severity stages. Additionally in patients suffering from milder forms of the disease, treatment with either topical corticosteroids (TCS), topical calcineurin inhibitors (TCI) or topical phophodiesterase 4 (PDE4) inhibitors are 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 (Eichenfield et al 2014, Sidbury et al 2014). Only in rare cases and transiently are oral corticosteroids used, as they are associated with side effects and a rebound effect. 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 globally approved systemic therapy for treatment of moderate to severe AD is dupilumab (anti-Interleukin 4 Receptor alpha (IL4Ra) antibody). According to Simpson et al (2016), in moderate to severe AD patients, a response rate of 38% was observed (compared to 10% for placebo) following 16 weeks treatment with dupilumab. This proportion of patients describes those who reach 0 (clear) or 1 (almost clear) on a 5-point Investigator Global Assessment (IGA) scale. Oral Janus kinase inhibitors are as well in late stage development, and seem to demonstrate similar efficacy as compared to dupilumab; however, they may have significant safety concerns, such as infection risks, risk of malignancies and thromboembolic events. Thus, there is still a high unmet medical need for additional systemic treatment options in moderate to severe AD patients.

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IL-18 (a downstream component of the inflammasome) is a pro-inflammatory cytokine associated with the induction of Th1 responses, enhanced type I macrophage activation and NK/$CD8^+$ T cell cytotoxicity. IL-18 levels are strongly correlated with AD disease severity, and its receptor (Interleukin-18 receptor 1: IL-18R1) expression is genetically associated with AD. IL-18 has been shown to also induce type 2 immune responses in Th2, T resident memory CCI cells which are regarded as key drivers of the type 2 immune response in AD.

Indeed, serum IL-18 levels are increased in AD patients, and correlate with disease severity (Thijs et al 2015, Zedan et al 2015, Gohar et al 2017). IL-18 was observed to be the single most overexpressed protein in the epidermis of pediatric AD patients and associated with AD disease activity (McAleer et al 2019, Hulshof et al 2019). In peripheral blood lymphocyte cultures from AD patients stimulated with staphylococcal enterotoxin B (SEB), IL-18 levels were significantly correlated with IL-4 levels and AD disease activity (SCORAD) (Suwarsa et al 2017).

In preclinical models such as Keratin 14 (K14)/IL-18 transgenic mice which overexpress IL-18 in keratinocytes in the skin, IL-18 contributes to the development of AD-like inflammatory lesions independently of IgE/STAT6 (Konishi et al 2002). Similarly, keratinocyte-specific Casp1 transgenic mice (K14Casp1Tg), which display high levels of mature IL-18, develop AD like itchy skin lesions with age (Tsutsui et al 2011; Yamanaka et al 2000) and blockade of IL-18 prevented Staphylococcus aureus induced AD-like disease model in mice (Terada et al 2006). *In vivo* administration of IL-18 causes Th2 differentiation and increases IgE production in a CD4+ T cell–, IL-4– and STAT6–dependent fashion in mice (Yoshimoto et al 2000; Hoshino et al 2000).

In addition, emerging genetic evidence further supports the causal relationship of IL-18 pathway and AD; the IL-18 receptor is one of the 5 top genes dysregulated in AD patients in a large Genome-wide association studies (GWAS) study on 21,000 cases and 95,000 controls (Paternoster et al 2015). Mendelian randomization applied to AD GWAS and serum pQTL data seems to causally implicate genetically-driven higher levels of IL18R1 as an increased AD risk (Sun et al 2018, McGowan et al 2019).

1.2 Purpose

The purpose of this proof of concept study is to determine whether CMK389 displays the safety and efficacy profile to support further development in participants with moderate to severe AD.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of CMK389 in participants with moderate to severe AD	• IGA response (defined as clear or almost clear and at least 2 point reduction from baseline) at Week 16
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety and tolerability of CMK389 in participants with AD	• Number, seriousness and frequency of adverse events over time

2.1 Primary estimands

The primary clinical question of interest is: What is the effect of the CMK389 treatment versus placebo on IGA response rate after 16 weeks of treatment in participants with moderate to severe AD without any relevant use of prohibited medication or use of rescue medication taken after the first 6 weeks.

Prohibited or rescue medication are relevant when their use may have a potential confounding effect on the efficacy assessment.

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without any relevant use of prohibited medication or use of rescue medication taken after the 6 first weeks.

The primary estimand is described by the following attributes:

1. Population: Adult participants with moderate to severe AD is the target population for biologics (Beck et al 2014, Simpson et al 2016) and is defined by an IGA score of moderate to severe (3 or 4) and an EASI score of at least 12. Further details about the population are provided in Section 5.
2. Primary variable: IGA response (defined as clear or almost clear and at least 2 point reduction from baseline) at Week 16.
3. Treatment of interest: the randomized treatment (the investigational treatment CMK389 or the placebo treatment) taken for the entire study duration without any use of prohibited medications or use of rescue medication taken after the first 6 weeks.
4. The summary measure: Treatment difference of the CMK389 and placebo in absolute responder rates.

Handling of remaining intercurrent events:

1. Use of rescue therapy (after first 6 weeks of treatment)
2. Use of prohibited medication to treat AD symptoms or with impact on efficacy
3. Study treatment discontinuation due to lack of efficacy
4. Study treatment discontinuation due to AE related to AD, e.g. worsening of AD
5. Study treatment discontinuation due to AE not related to AD or due to lack of tolerability
6. Study treatment discontinuation due to other reasons (e.g. administrative if participant relocates to a region where the trial is not offered, or withdrawal of informed consent)

For the intercurrent events 1 to 4, a composite strategy will be used: use of any therapy (prohibited or rescue medication taken after the first 6 weeks) as well as any study treatment discontinuation due to lack of efficacy or due to AE related to AD are considered as unfavorable outcome, i.e. the participant will be treated as a non-responder.

For the intercurrent events 5 to 6, a treatment policy strategy will be used and the intercurrent event will be ignored.

2.2 Secondary estimands

Not Applicable.

3 Study design

This is a randomized, placebo-controlled, parallel-group, non-confirmatory, investigator and participant blinded study in adult participants with moderate to severe AD.

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Approximately 64 eligible participants with moderate to severe AD will be randomized into one of four treatment arms (randomization 4:1:2:1):

- Arm 1: 32 participants treated i.v. with 10 mg/kg CMK389
- Arm 2: 8 participants treated i.v. with placebo
- Arm 3: 16 participants treated s.c. with 300 mg CMK389
- Arm 4: 8 participants treated s.c. with placebo

The study will include adult participants with moderate to severe AD. For details please refer to inclusion/exclusion criteria in Section 5.

After confirmation of eligibility, participants will be included in one of the above mentioned arms. Efficacy over time will be measured by the clinical scores, such as IGA

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Safety will be monitored throughout the study by physical exams, vital signs, ECG recordings, adverse events and safety laboratory monitoring. Refer to Assessment schedule (Section 8) for details.

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4 Rationale

As this is the first time that an anti-IL18 compound is tested in AD participants, the goal is to demonstrate preliminary efficacy of CMK389. To avoid any bias associated with an open label study, a placebo controlled study offers not only the option to compare to participants without relevant interfering treatment but also the possibility of a double blind study, as study supplies can be packaged and labeled accordingly. As CMK389 is administered by two routes of administration, i.v. and s.c., the placebo group is also split into i.v. and s.c. administrations to ensure a double blind design.

In order to reduce the number of participants exposed to placebo, a randomization of 4:1:2:1 (CMK389 i.v., placebo i.v., CMK389 s.c., placebo s.c.) has been chosen.

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The comparison to placebo in this double blind, prospective and randomized trial allows comparison with many other studies conducted in AD, in particular using biologics, such as the SOLO studies with dupilumab (Beck et al 2014, Simpson et al 2016). Placebo controlled studies have been and still are conducted in adult AD at later development stages and in larger numbers; e.g. studies with lebrikizumab (see ClinicalTrials.gov Identifier: NCT04146363 and NCT04178967) or nemolizumab (Ruzicka et al 2017) (and see also ClinicalTrials.gov Identifier: NCT03985943 and NCT03989349) or with upadacitinib (see ClinicalTrials.gov Identifier: NCT03568318 and NCT03569293). In particular in AD, two recent open label proof of concept trials have shown initial signs of efficacy (Yi-Ling et al 2019, Diamant et al 2018), but no efficacy was observed when studied in well conducted, double blind, placebo controlled studies.

The study population of adult participants with moderate to severe AD is the target population for biologics (Beck et al 2014, Simpson et al 2016). To be eligible for inclusion in this trial, patients need to have an AD severity defined by an IGA score of moderate to severe and an EASI score of at least 12 as well as a minimum of 3 in the pruritus numerical rating scale (NRS). This mimimum score is a bit lower than previous large trials in moderate to severe AD (inclusion criteria of EASI 16, see Simpson et al 2016, Guttman-Yassky et al 2020a, Guttman-Yassky et al 2020b) in order to facilitate recruitment without compromising the scientific outcome. Furthermore, a similar threshold has also been used previously in other Phase 2 trials with biologics (Wollenberg et al 2019 and Simpson et al 2019). Prior to enrollment in this trial treatments of AD and systemic immunosuppressives, including steroids, are washed out, using typical and relevant wash out periods. Only topical non medicated emollients are allowed to be used.

This study is only open for adult participants, as safety data for a younger populations have not yet been collected and preliminary efficacy in adults is not yet established. At the time of protocol preparation, only adult healthy volunteers have been exposed to CMK389, and a proof

of concept trial in adult participants in pulmonary sarcoidosis is planned to be conducted in parallel.

4.1 Rationale for study design

Table 4-1 Rationale for study design

Placebo controls	The placebo group is used to define the natural history of disease under the study's conditions. Comparison of placebo to the active group provides the most rigorous test of efficacy. The comparison to placebo is being used for many studies including late stage development trials (Simpson et al 2016, Guttman-Yassky et al 2020a,Guttman-Yassky et al 2020b,Wollenberg et al 2019, Simpson et al 2019) to enable a rigourous and double blind comparison. In this study, placebo exposed participants are reduced to a quarter of overall study population. Commercially Confidential Information Participants may use emollients as basis therapy during the study, and may use oral antihistamines for symptomatic itch relief. If medically justified and disease severity is worsening, participants may use other rescue treatments (standard of care) as well.
Randomization	Randomization is used to avoid "selection bias" in the assignment of participants to treatment groups. Randomization also serves to balance the treatment groups with respect to many known and unknown confounding variables; and randomization forms the basis of assumptions for our statistical tests. In this study randomization was set up so as to favor recruitment of participants in treatment arm 1 (CMK389 i.v. administration).
Blinding	Conscious and unconscious biases are avoided within treatment arms ("detection bias" and "reporting bias", pertaining to outcome assessment) by ensuring that participants and investigators are unaware of the treatment assignment. As CMK389 is administered as an i.v. and a s.c. drug, the corresponding placebo will be administered as i.v. and s.c. to ensure double blind design. Thus the above described biases will be limited to the minimum, as investigators and participants will be blinded if the participant will receive active or placebo. However, investigators and participants will not be blinded to the route of administration either i.v. or s.c, but will not know whether the participant is in the active or placebo group. As the study drugs are supplied to the site as bulk supplies, an unblinded pharmacist or a nurse or delegate is needed to prepare the drug supplies and may not discuss any details with the personnel directly in contact with the participant.
Duration of treatment	Commercially Confidential Information This treatment duration is expected to provide information about efficacy of CMK389 in the AD participant population and is in line with currently conducted placebo controlled large trials with systemic treatments in AD which are between 12 and 16 weeks of treatment with biologics (Simpson et al 2016, Ruzicka et al 2017, Guttman-Yassky et al 2020a, Guttman-Yassky et al 2020b).

4.2 Rationale for dose/regimen and duration of treatment

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The chosen timepoint of 16 weeks for the primary endpoint is in alignment with many randomized controlled studies in AD using biologics, in particular with the phase 3 trial of dupilumab (Simpson et al 2016, Guttman-Yassky et al 2020a, Guttman-Yassky et al 2020b).

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CMK389 300mg s.c. dosing is added to the study to support a second dose level and generate data to develop the s.c. route of administration in late stage studies.

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Statistically, the study is adequately powered to test the efficacy of CMK389 i.v. versus placebo. CMK389 s.c. will be descriptively compared to placebo, but there will be no formal statistical test.

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

In this study, the corresponding placebo to CMK389 will be used as comparator to provide objective evidence of clinical efficacy and enable a double blind comparison to avoid unconscious biases associated with uncontrolled studies. To establish clinical efficacy in a proof of concept study, where the use of a placebo control is established even in phase 3 studies for up to 16 weeks, is one of the highest scientific standards for early studies. The placebo controlled design will as well provide objective evidence to compare safety and pharmacodynamic (PD) data and provide the opportunity to historically compare to other placebo controlled trials.

Participants will need to be washed out from the concomitant treatment, but can continue basic therapy with emollients and may also use oral antihistamines for symptomatic relief of itch. If study participants experience any worsening of AD, the investigator can initiate rescue treatment or treatment discontinuation, if medically justified.

As CMK389 is administered using the i.v. and s.c. route, to keep the blind placebo is also administered using the i.v. and s.c. route.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

CMK389 is a CCI targeting IL-18, a mechanism of action (MoA) that has not yet been tested in AD. There is thus no proven direct medical benefit for participants who will participate in this study as this is the first time CMK389 is administered to AD participants.

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CMK389 has not yet been tested in any studies in patients,

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No clear dose relationship was established for adverse events or organ classes such as infections, or gastro-intestinal disorders, nor in safety laboratory monitoring.

Clinical studies with compounds with a similar MoA, such as Interleukin-18 Binding Protein (IL-18BP) or IL-18 antagonists (such as tadekinig, GSK-1070806 or AEVI-007/MEDI2338) have been conducted in adult Still's disease (AOSD, Gabay et al 2018, Kiltz et al 2020). Tadekinig is currently in later stage development in macrophage activation syndrome associated with NLR family CARD domain containing 4 (NLRC4) mutation and X-linked inhibitor of apoptosis protein (XIAP) deficiency (ClinicalTrials.gov Identifier: NCT03113760). Other completed studies incude chronic obstructive pulmonary disease (COPD, NCT01322594), diabetes (McKie et al 2016) or transplant participants (NCT02723786). Studies in Crohn's disease and Behcet disease are currently running or of unknown status (NCT03681067, NCT03522662). To our knowledge, none of the studies had significant safety issues; the transplant study was terminated due to lack of efficacy.

CMK389 is being developed for its expected immunomodulating activity. Participants treated with CMK389 may be at an increased risk of infection.

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In addition, administration of CMK389 carries the risk of anaphylaxis and/or hypersensitivity-type reactions. Commercially Confidential Information

Participants with a history of hypersensitivity to any components of the drug product or with a history of anaphylaxis or serious hypersensitivity syndrome will be excluded.

The risk of an overdose is limited as the drug will be administered by the study personnel and not by the participant.

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WoCBP 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 requirements outlined in the exclusion criteria. Only WoCBP who take highly effective contraception can participate in the trial. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Blocking IL-18 with CMK389 may impair the innate and cytotoxic immune responses that play a role in viral clearance. IL-18 contributes to antiviral immune responses by promoting interferon-gamma production by T cells, natural killer cells, and natural killer T cells and supports the induction of cytotoxic T cells. Impaired cytotoxic T cell responses may impair the killing of virus-infected cells. CMK389 should not impair the production of SARS-CoV-2 specific antibodies. However, the inflammasome and the pivotal mediators IL-1β, IL-18, and NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) contribute to the hyper-inflammatory response that results in severe pulmonary tissue damage after initial SARS-CoV and SARS-CoV-2 infections. Patients with severe COVID-19 and respiratory failure have elevated levels of IL-1β and its downstream cytokine IL-6, as well as interferon-gamma (IFNγ) and IP-10 (CXCL10), both downstream markers of IL-18 pathway activation.

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To minimize these potential risks, appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific stopping rules, are included in this protocol.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over the period of 28 weeks from each participant as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule Section 8.

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See the Section 8.5.3.1 on the potential use of residual samples.

5 Study Population

The study population will consist of adult female and male participants with moderate to severe AD. It is planned to randomize approximately 64 participants globally.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Adult male or female participants with chronic atopic dermatitis, according to the American Academy of Dermatology Consensus Criteria (Eichenfield et al 2014), aged 18 to 65 years, present for at least 1 year before screening.
4. Moderate to severe AD defined as:
   - IGA score of ≥ 3 (on a scale of 0 to 4, in which 3 is moderate and 4 is severe) at Baseline (or Screening if Baseline is omitted).
   - EASI score of ≥ 12 at Baseline (or Screening if Baseline is omitted).
   - Pruritus (NRS) of at least ≥ 3 at Baseline (or Screening if Baseline is omitted).
5. Participants who are candidates for a systemic therapy, defined as e.g. inadequate response to treatment with topical medications, or for whom topical treatments are otherwise medically inadvisable (e.g. because of important side effects or safety risks, patients with large affected body surface areas) as assessed by the investigator.
6. Participants must have a body mass index (BMI) at screening within the range of 18 to ≤35 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2. No rounding of calculated BMI value to nearest integer should be done when assessing for eligibility.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Any skin disease that, in the opinion of the investigator, would confound the diagnosis or evaluation of AD disease activity (e.g., Netherton Syndrome, or other ichthyoses, cutaneous T-Cell Lymphoma, extensive contact dermatitis, chronic actinic dermatitis and other forms of eczema, such as seborrheic and microbial eczema).
2. Participants taking prohibited medication not completing the wash out period as specified in Table 6-2.
3. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.

4. Any active, recent or recurrent systemic or localized infection at screening or prior to first treatment which in the opinion of the investigator immunocompromises the participant and/or places the participant at unacceptable risk for immunomodulatory therapy, such as:
   - Any acute bacterial, fungal, or viral (e.g. herpes simplex, herpes zoster, chicken pox) skin/mucosal infection that has not resolved within 2 weeks prior to first treatment or within 12 months in case of ezcema herpeticum.
   - Clinically infected AD within 4 weeks prior to first treatment.
   - Any other infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to first treatment.
   - Tuberculosis (TB):
     - Evidence of active or latent tuberculosis (TB) infection, as determined by Quantiferon test at screening (Note: if Quantiferon test is indeterminate, it may be repeated once. Two indeterminate Quantiferon tests will be considered as evidence of TB infection. Furthermore, after anti-TB treatment, participants with history of or latent TB may become eligible according to national guidelines).
   - Human Immunodeficiency Virus (HIV):
     - History of primary or secondary immunodeficiency, or a positive HIV (Chemiluminescence and Polymerase Chain Reaction test result.
   - Hepatitis B:
     - Positive hepatitis B surface antigen (HBsAg) and/or positive hepatitis B core antibody (anti-HBc).
   - Hepatitis C:
     - positive hepatitis C antibody (anti-HCV), unless it can be documented that the participant has received highly-effective HCV-specific antiviral therapy, HCV RNA levels are measured, and HCV RNA is undetectable at least 12 weeks after conclusion of HCV-specific antiviral therapy.
5. Any other current or past clinically significant medical condition, including psychiatric condition, which in the Investigator's opinion may interfere with safety of the participant, study objectives or adherence to the protocol.
6. Participants with confirmed abnormal absolute neutrophil count (ANC) of $<1.5 \times 10^9$/L or with thrombocytopenia of $< 75.0 \times 10^9$/L at screening and baseline (unless baseline visit is omitted).
7. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
8. History of hypersensitivity to any component of the study drug product, or to drugs of similar chemical classes (i.e., IgG-1 related biologic agents).
9. History of severe or serious allergy or hypersensitivity reactions, such as anaphylactic shock, asthma, or uncontrolled urticaria.
10. Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
11. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

12. Women of child-bearing potential (WoCBP), defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 6 months after last dose. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. 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 study treatment. 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 participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

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

    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 bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing and taking study treatment are outlined in the Pharmacy Manual.

6.1.1 Investigational and control drugs

Table 6-1 Overview of study medication

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor
CMK389 150mg	Powder for solution for injection/infusion	Intravenous use Subcutaneous use	Open label bulk supply; vials	Novartis
CMK389 Placebo	5% Dextrose Solution or 5% Glucose Solution	Intravenous use	Infusion bags only	Locally procured by sites
CMK389 Placebo	Solution for Injection	Subcutaneous use	Open label bulk supply; vials	Novartis

6.1.2 Additional study treatments

No other treatment beyond investigational drug and placebo control drug are included in this trial.

6.1.3 Treatment arms/group

Participants will be randomized to one of the following 4 treatment arms in a ratio of 4:1:2:1

- Arm 1: CMK389 10 mg/kg i.v.
- Arm 2: Placebo i.v.
- Arm 3: CMK389 300 mg s.c
- Arm 4: Placebo s.c.

6.2 Other treatment(s)

Not applicable.

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including use of medicated and non medicated emollients used for AD, physical therapy, blood transfusions, vaccination) administered after the participant was enrolled into the study must be recorded on the appropriate electronic Case Report Forms (eCRFs).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Norvartis to determine if the participant should continue participation in the study.

6.2.2 Prohibited medication

Table 6-2 Prohibited medication

Medication	**Prohibition period (Wash-out)**	**Action taken if taken in the prohibition period**
Non-biologic systemic immunosuppressive and/or anti-inflammatory treatments for treatment of AD including but not limited to systemic corticosteroids (e.g. i.v., i.m. or oral)*, cyclosporine, tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, as well as leukotriene inhibitors (such as montelukast), oral phosphodiesterase 4 (PDE4) inhibitors (such as apremilast), and oral Janus kinase (JAK) inhibitors (e.g. baricitinib) Adrenocorticotropic hormone analogs	Within 4 weeks (or 3 months for i.m. administered corticosteroids) prior to first dose of CMK389 until End of Treatment (EoT)	Wash-out : do not randomize Treatment: discontinue study drug Follow-up: to be discussed on case by case basis
Any biologic therapy to treat AD	3 months prior to first dose of CMK389 until EoT	Wash-out : do not randomize Treatment: discontinue study drug Follow-up: to be discussed on case by case basis
Other biologic therapy (such as but not limited to etanercept, adalimumab, infliximab, omalizumab, secukinumab) with the exception of insulin and botulinum toxin.	3 months or 5 x half-lives (whatever is longer) prior to first dose of CMK389 until EoT	Wash-out : do not randomize Treatment: discontinue study drug Follow-up: to be discussed on case by case basis

Medication	**Prohibition period (Wash-out)**	**Action taken if taken in the prohibition period**
Live Vaccination	3 months prior to first dose of CMK389 until EoS	Wash-out: do not randomize Treatment: discontinue study drug Follow-up: to be discussed on case by case basis
Topical corticosteroids (TCS) of higher potency than lowest potency TCS (e.g. hydrocortisone)** Topical calcineurin inhibitors (TCI)** Topical phosphodiesterase 4 (PDE4) inhibitor (e.g. Crisaborole)** Topical JAK inhibitors	2 weeks prior to first dose of CMK389 until EoT	Wash-out: do not randomize Treatment/Follow up: to be discussed on case by case basis
Topical corticosteroids (TCS) of lowest potency (e.g. hydrocortisone)** Other topical medicated treatment for AD such as tar, antimicrobials, bleach baths, etc. Note: Non-medicated emmolients including medical device creams (such as Atopiclair®) are permitted.	1 week prior to first dose of CMK389 until EoT	Wash-out : do not randomize Treatment: discontinue study drug Follow-up: to be discussed on case by case basis
Phototherapy, tanning booths or excessive sun exposure	4 weeks prior to first dose of CMK389 until EoT	Wash-out: do not randomize Treatment: discontinue study drug Follow-up: to be discussed on case by case basis
Any Investigational Treatment	Within 5 half-lives of Baseline or until the expected pharmacodynamic effect has disappeared, whichever is longer; or longer if required by local regulations	Wash-out: do not randomize, and rescreen participant after wash-out if the recruitment period is still ongoing Treatment: discontinue study drug Follow-up: to be discussed on case by case basis

* Inhaled corticosteroids (CS) or nasal sprays and eye drops are not considered systemic immunosuppressive treatment.
**Rescue therapy used as per Section 6.2.3 (only if medically necessary i.e., to control intolerable AD symptoms, as assessed by investigator) is not considered a prohibited medication.

6.2.3 Rescue medication

Rescue treatment may be needed if participants experience an AD flare. As a basis therapy, participants should be advised to use emollients as needed, if these are non-medicated topical formulations. If pruritus occurs, and is causing moderate to severe itch, oral H1-antihistamines may be considered. The Investigator is advised to avoid prescribing any medicated rescue treatment between week 12 and 16.

However, if a flare occurs, and if it is medically indicated, transient use of topical treatments, such as topical calcineurin inhibitors (TCI), topical phosphodiesterase 4 (PDE4) inhibitor, or low to mid potent topical corticosteroids (TCS) (i.e. not higher potency than mometasone furoate cream 0.1% or similar) may be used before week 12. If possible use the topical treatment on the most affected areas and restrict use to these areas. The use of these rescue treatments must be reported as concomitant therapies and on what anatomical areas these were used.

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If the need for rescue therapy arises between scheduled study visits, the participant may come for an unplanned visit for the investigator to assess the participant. Investigators must remind participants that they should use rescue medication only if really needed (i.e. to control intolerable AD symptoms) and only when instructed by the investigator because the use of rescue medication may affect the validity of study results negatively. Rescue medication use must be stopped as soon as not needed anymore as assessed by the investigator.

After a participant is given rescue medication, in particular topical treatments, the participant 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 recorded in the appropriate eCRF.

Medically indicated treatments should be initiated in the interest of the participant, whenever an adverse event occurs, but no specific treatments are recommended.

6.2.4 Restriction for study participants

Participants should be informed and reminded of the restriction of topical and systemic treatments for AD. Please refer to Section 6.2.3 (Rescue medication), if participants need to report these medications and the quantity used to the site personnel, which will be recorded in the eCRFs.

In addition, participants should be reminded that excessive sun exposure should be avoided as much as possible. Thus, visits to sun tanning or UV parlors and/or sun bathing are not allowed until after week 16.

If participants are allergic, they should be reminded that they should signal all known allergies in order to be able to track possible trigger factors for AD flares. Participants should be instructed to avoid any known allergens, when possible.

6.2.4.1 Dietary restrictions and smoking

Participants should be reminded to fast (having had their last meal the evening, approx 6-12 hours before visit) at all visits before coming to the site for clinical chemistry blood sample.

6.2.4.2 Other restrictions

The use of emollients as outlined in Section 6.2.3 should not be carried out for at least 2 hours before clinical assessments and CCI are done.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is uniquely identified in the study by a Participant Number (Participant No.), which is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. Once assigned, the Participant No. will not be reused. The Participant No. consists of the Center Number/Site Number (as assigned to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form (ICF), the participant is assigned to the next available sequential Participant No.

Example: 1001001, 1001002, etc. where "1001" is the center number/site number and "001", and "002" are the sequential incrementing participant numbers.

6.3.2 Treatment assignment, randomization

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the Novartis IRT (NIRT), using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

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

The overall randomization ratio will be 4:1:2:1 (CMK389 i.v., placebo i.v., CMK389 s.c., placebo s.c.). Commercially Confidential Information

6.4 Treatment blinding

This is a participant and investigator-blinded study. Participants and investigators will remain blinded to study treatment throughout the study, except where indicated below.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site.

Drug product will be supplied in bulk, so an unblinded pharmacist (or other qualified and trained staff preparing study drug for administration) who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive a randomization list or treatment allocation cards from Novartis Global Clinical Supply (GCS) with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff

The following unblinded sponsor roles are required for this study

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) (PK, IG)

The unblinded field monitors are required to review drug accountability and allocation at the site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual participants. The unblinded monitors will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

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Study programmers and other personnel involved in study data analysis CCI are allowed to access treatment assignment information for the purpose of conducting interim analyses.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-3 Blinding and unblinding plan

	Time or Event		
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single participant unblinded)**
Participants	B	B	UI
Site staff	B	B	UI
Unblinded site staff (see text for details)	B	UI	UI
Global Clinical Supply and Randomization Office	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI
Unblinded Pharmacovigilance sponsor staff	B	UI	UI
Statistician/statistical programmer/ data analysts	B	B	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	UI	UI	UI
All other sponsor staff not identified above	B	B	UI

Key:

UI: Allowed to be unblinded on individual participant level

B: Remains blinded

NA: Not applicable to this study

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Study medication will be administered at site. Any deviations from protocol mandated dose are to be recorded in eCRF.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with CMK389 as detailed in Section 8.5.2.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs), as no specific AE have been detected with CMK389. Participants are required to undergo observation for maximum of one hour post-infusion prior to leaving site (or longer if deemed necessary by the investigator).

Acute infusion or hypersensitivity reactions: In the event of an acute infusion or hypersensitivity reaction, the investigator should consider the criteria for treatment discontinuation (Section 9.1.1), and the participant should be treated with antihistamines and glucocorticoids. Depending on severity, participants may also require supplemental oxygen, volume expansion, catecholamines and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of CMK389 may be considered dependent on the participant's condition. Participants should be observed for at least four hours after resolution of signs and symptoms; and those who have experienced severe infusion reactions should be closely observed for 24 hours after resolution because of the risk for a biphasic episode.

Infections: In the event of an infection, the investigator should consider the criteria for treatment discontinuation (Section 9.1.1), as well as consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof (e.g., antiviral treatment for herpes simplex or zoster) in consultation with infectious disease experts, as appropriate.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to do so in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the NIRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant 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 NIRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- participant number

In addition, oral and written information to the participant 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.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given participant and, if applicable, whether the participant can continue with follow up assessments.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under Section 6.1.1 (Investigational and control drugs). Please refer to Pharmacy manual for detailed instructions about study medication preparation and administration.

As per the treatment assigned to the participant, investigator staff will select the study treatment to dispense to the participant. The study medication has a label. A unique medication number is printed on the study medication label.

6.7.1 Handling of study treatment and additional treatment

Study treatment must be received and acknowledged by a designated staff at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site staff have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Pharmacy Manual.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

An unblinded pharmacist or other qualified and trained site staff are required to prepare the study drug and placebo for administration. Please refer to the pharmacy manual for details.

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 participant 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.

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.

In this study there is no additional treatment apart from study treatment.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

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 participant source documents.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant 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 (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also include:

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  - As applicable, Pregnancy Outcomes Reporting Consent for female participants

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WoCBP 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 requirements.

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A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

The Assessment Schedule lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed (EoS/Early discontinuation visit). At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications should be recorded on the eCRF.

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsultation) or visits by site staff/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again.

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8.1 Screening

If participant failed initial screening, re-screening of the participant is allowed after consultation with Sponsor.

In the case where a safety laboratory assessment at screening and/or baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

Local guidelines and regulations need to be strictly followed regarding the screening and monitoring of the SARS-CoV-2 (COVID-19).

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).

Screening for Hepatitis C will be based in HCV antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site e.g. Polymerase Chain Reaction.

Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator. Results will be available as source data and will not be recorded within the eCRF. All samples will be shipped to the central laboratory.

8.1.1.2 Quantiferon Test

Blood tuberculosis testing with the Quantiferon assay (QuantiFERON®-TB Gold In-Tube) will be performed as specified in the Assessment schedule in Section 8. For the details regarding sample preparation and shipment please refer to the laboratory manual.

Note: if Quantiferon test is indeterminate, it may be repeated once. Two indeterminate Quantiferon tests will be considered as evidence of TB infection. Furthermore, after anti-TB treatment, participants with history of or latent TB may become eligible according to national guidelines.

Any significant findings will be recorded in the "Relevant medical history/Current medical conditions" section of the eCRF.

8.1.2 Information to be collected on screening failures

Participants who sign an ICF and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The visit date, demographic information, informed consent (and withdrawal of informed consent, if applicable), SAE, Death (if applicable) pages must also be completed for screen failure participants who experience SAE. No other data will be entered into the clinical database for participants who are screen failures and experience no SAE. (see

Section 10.1.3. SAE reporting for details). If the participant fails to be randomized, the NIRT must be notified within 2 days of the screen failure that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Participant demographics/other baseline characteristics

Participant demographics: age, sex, race, predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

Severity of AD will be measured by Clinical Outcomes Assessments (COAs) such as IGA (Investigator Global Assessment); Commercially Confidential Information

The primary endpoint is IGA response at week 16.

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8.3.1 IGA

The IGA scale used in the study is vIGA-AD™ (Validated Investigator Global Assessment scale for Atopic Dermatitis). The IGA rating scale is used to determine the severity of AD symptoms and clinical response to treatment. It reflects a participant'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.

IGA response is defined as clear or almost clear after week 16 with at least a 2 point-reduction from baseline.

The scale is a static scale and does not refer to previous status of the participant. The Investigator or trained qualified designee will complete the IGA assessment on each of the visits as outlined in the Assessment Schedule. Whenever possible, the IGA assessments should be performed by the same evaluator throughout the study.

The IGA should always be conducted as the first clinical assessment, CCI . It must be based on a whole body skin inspection.

Table 8-4 Investigator Global Assessment (IGA)

Score	Morphological Description
0 - Clear	No inflammatory signs of atopic dermatitis (no erythema, no lichenification, no oozing/crusting). Postinflammatory 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 and bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

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8.3.4 Appropriateness of efficacy assessments

The efficacy measurements included in this study have been and are used in clinical trials evaluating efficacy in AD and are standard for this indication (Eichenfield et al 2014, Simpson et al 2016, Beck et al 2014, Chopra and Silverberg 2018).

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

During the COVID-19 pandemic that limits or prevents on-site study visits regular phone or virtual calls may occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

For details on AE collection and reporting, refer to Section 10.1.1 Adverse Events.

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and vital signs (Systolic and Diastolic Blood pressure [SBP and DBP] and pulse). A short physical exam will be done at Day 29 visit except at visit at Baseline/Day 1 and at Day 113 when complete physical examination will be completed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

Assessment	Specification
Vital signs	Vital signs will include the collection of tympanic body temperature (recorded in °C), blood pressure (BP) and pulse measurements. After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If vital signs are out-of-range at screening and/or baseline two additional readings can be obtained, so that up to three consecutive assessments are made, with the participant seated quietly for approximately five minutes preceding each repeat assessment. In case of repeated vital assessments, the eCRF should contain all repeat measurements.
Height and weight	Height is obtained in centimeters (cm) and body weight is obtained in kilograms (kg) and rounded to the nearest 0.1 kg. Weight is obtained in indoor clothing, without shoes. Body mass index (BMI) will be calculated using the following formula: • BMI = Body weight (kg) / [Height (m)]2 Screening visit weight will be used for dose calculations by the pharmacist.

8.4.1 Laboratory evaluations

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with the sponsor, if considered relevant by PI) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

A central laboratory will be used for analysis of all safety specimens collected. In case of need for clarification or follow-up on adverse event or liver/renal event, local laboratory might be used in addition to central laboratory assessment. Results from all local laboratory re-testing should be entered in appropriate eCRF pages. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

Participants should be reminded to fast (having had their last meal the evening, approx. 6-12 hours before visit) at all visits before coming to the site for clinical chemistry blood sample.

Clinical Chemistry

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials (neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count
Chemistry	The chemistry panel (fasting at all visits) will include: albumin, alkaline phosphatase, total and differentiated bilirubin, calcium, chloride, serum bicarbonate, creatinine, creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase, γ- glutamyltransferase (GGT), glucose, sodium, potassium, inorganic phosphorus, total protein, lactate dehydrogenase (LDH), magnesium, blood urea nitrogen (BUN), uric acid, lipase, triglycerides, cholesterol (direct LDL, HDL cholesterol and LDL cholesterol) and serum ketones. The chemistry panel will also include total immunoglobulin E (IgE) and high sensitivity C-reactive Protein (CRP) as specific markers for AD.
Urinalysis	Semi-quantitative 'dipstick' evaluation of the urine for the following parameters will be performed centrally: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood. If the dipstick result is positive for nitrite, leucocytes and/or blood, microscopic analysis will be done (including white blood cells, red blood cells and casts). Urine culture and sensitivity test may be performed locally as per investigator's discretion.
Hepatitis and HIV markers	anti-HIV antibody, HBsAg, anti-HBc, anti-HCV, HCV RNA(if applicable)
Pregnancy test	Serum / Urine pregnancy test (refer to Section 8.4.3 Pregnancy and assessments of fertility)

8.4.2 Electrocardiogram (ECG)

ECGs will be analyzed locally and performed with ECG machines at the investigator sites. Investigator sites will follow their own procedures relating to the ECG collection and reporting.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Single 12-lead ECGs are collected and results are entered into the appropriate eCRF page. The original ECGs appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, participant initials, participant number, date and time, and filed in the study site source documents. Investigator should document clinical evaluation in source. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.4.3 Pregnancy and assessments of fertility

All WoCBP will have pregnancy testing during the study until EoS at the defined assessment visits. As additional follow up period is required for screening of pregnancy, a monthly urinary pregnancy test must be conducted for 6 months after the last dose of study drug. More urinary tests can be done at the discretion of the investigator. A home urine pregnancy test kit will be provided to participants by the site.

WoCBP should be instructed to use highly effective contraception during the study and after EoS (for 6 months after the last dose of study drug).

At EoS, the site will ask the participant to conduct the pregnancy test(s) as defined in assessment schedule Table 8-3 and will call the patient to remind her. The participant should communicate the results of the pregnancy test(s) to the site. A positive pregnancy test must trigger a pregnancy report to the sponsor (see Section 10.1.4). If pregnancy is discovered after EoS, the participant should be asked to come for a visit to the site and to read and sign the pregnancy consent form to allow the Study Doctor to ask about her pregnancy.

Assessments of fertility:

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy.
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

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9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited medication Section 6.2.2 and rescue medication Section 6.2.3
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding
- Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion or injection to administer study treatment is required in such cases.
- For liver events, please see Section 10.2.1. For renal events, please see Section 10.2.2
- If a liver or renal event occurs, follow guidelines outlined in Section 16.2 and Section 16.3 regarding discontinuation of study treatment.

The reasons for treatment discontinuation must be collected in line with the intercurrent events introduced in Section 2.1 and the “treatment” attribute described in Section 2 and Section 6.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 'Withdrawal of Informed Consent' section). Where possible, they should return for the assessments indicated in the Assessment Schedule in Section 8. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section (Section 9.1.3). This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the NIRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code Section 6.6.3.

9.1.1.1 Replacement policy

Participants may be replaced until the study has 64 total evaluable participants. The evaluability of the participant will be defined by availability of baseline data and suitable EoT visit data as well as the administration of at least 3 out of 4 doses of the study drug. If any patient discontinues treatment because of prohibited medication (refer to Section 6.2.2), the patient will not be replaced and will be considered as a non-responder for the primary analysis.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

Where consent to the use of personal and coded data is not required, the participant cannot withdraw consent. They still retain the right to object to the further use of personal data.

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 participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table in Section 8.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants 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 participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

Enrollment in the study will be placed on hold if any of the following occurs cumulatively across all of the cohorts:

- Two or more drug related Serious Adverse Events (SAEs);
- Two or more participants experience hypersensitivity reactions or injection reactions of moderate to severe intensity;
- Two or more participants experience a similar AE which was assessed as severe in intensity and are considered as potentially related to the study treatment;
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold.

The study may resume following a safety review, if the Investigators and Sponsor agree it is safe to proceed. Any restart of the study following a full safety review will require notification to health authorities or submission and approval of a substantial amendment, whichever is appropriate based on local requirements.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant’s interests. The investigator or sponsor depending on local regulation 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 participant finishes their End of study (EOS) visit for males and females of not child bearing potential (EOS V199 or V299) and for WoCBP [EOS (V199 or V299) and V399], 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. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

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 clinical investigation participant after providing written informed consent for participation in the study until the end of the study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

AEs of Special Interest comprise hypersensitivity reactions such as serum sickness and anaphylaxis (as defined by Sampson criterion #1; Sampson et al 2006).

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 10.1.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant 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 should 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 participant with underlying disease. Investigators have the responsibility for managing the safety of individual participant and identifying adverse events. Alert ranges for liver and kidney related events are included in Section 16.2 and Section 16.3 respectively.

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

1. The severity grade
    a. Adverse events will be primarily assessed and graded according to the "*Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*". A copy of the Toxicity Grading Scale can be found in the Investigator Portal.
    b. For any adverse event not listed in the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", the adverse event will be assessed and graded according to the "Common Terminology Criteria for Adverse Events", version 5.0 (CTCAE v5.0). A copy of the CTCAE Grading Scale can be found in the Investigator Portal.
    c. For infusion-related reactions, event will also be assessed and graded according to the CTCAE v5.0
2. Its relationship to the study treatment
    - Yes or
    - No
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding investigational treatment.

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

- no action taken (e.g. further observation only)
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- participant hospitalized/participant's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved, recovered/resolved with sequelae; fatal; or unknown)

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

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure. This information will be included in the participant informed consent and should be discussed with the participant 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 IN or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the participant.

The investigator must also instruct each participant to report any new event (beyond the protocol observation period) that the participant, or the participant'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.

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

10.1.2 Serious adverse events

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - 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 participant's general condition
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met. Life-threatening in the context of a SAE refers to a reaction in which the participant 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 ICH E2D Guideline 2004).

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 participant or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH E2D Guideline 2004).

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 on the eCRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 10.1.3.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay (and under no circumstance later than within 24 hours) of learning of its occurrence *(Note: If more stringent, local regulations regarding reporting timelines prevail).* Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen Failures and Run-In Failures (e.g. a participant who is screened but is not treated or randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

For participants considered Run-In Failures, SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Run-In Failure must be reported to Novartis.

Randomized OR Treated Participants: SAEs collected between time participant signs ICF until 30 days after the participant has discontinued or stopped study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay (and under no circumstance later than within 24 hours) of the investigator receiving the follow-up information *(Note: If more stringent, local regulations regarding reporting timelines prevail)*. 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.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an 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.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant 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.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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, participant 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 recorded on the appropriate 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 within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing 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

For more information on AE and SAE definition and reporting requirements, please see the Section 10.1.

10.2 Additional Safety Monitoring

Not applicable.

10.2.1 Liver safety monitoring

To ensure participant 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.

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

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-1. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation within 48-72 hours.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory in timely manner, then the repeats can also be performed additionally at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1 Discontinuation of study treatment section), if appropriate.
- Hospitalization of the participant if appropriate.
- Causality assessment of the liver event.
- Thorough follow-up of the liver event should include:
- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x Upper Limit of Normal (ULN), fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the participant is asymptomatic. Retesting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 16-3.
- Imaging such as abdominal US, CT or MRI, as appropriate.
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Section 16.3.

All follow-up information, and the procedures performed must be recorded as appropriate in the eCRF.

10.2.3 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 assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

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 the data 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 participant data for archiving at the investigational site.

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

11.2 Database management and quality control

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

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

Concomitant treatments and prior 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. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

Screenings, randomizations, as well as randomization codes and data about all treatment arms assigned to the participant will be tracked using an Interactive Response Technology (IRT).. The system will be supplied by Novartis, who will also manage the database. The data will be sent electronically to Novartis team (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.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. 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 Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

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 participants will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment received.

The safety analysis set will include all participants who received any study drug.

The PK analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug.

The PD analysis set will include all participants who received any study drug and had no protocol deviations with relevant impact on PD data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure to study treatment will be summarized by treatment group. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group. Additionally, rescue therapy as well as concomitant anti-histamines will be summarized by treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary aim of the study is to assess efficacy of CMK389 in participants with moderate to severe AD. This will be evaluated by assessing the IGA response at Week 16. This analysis will be performed on the PD analysis set. For the efficacy analyses, the two placebo groups (placebo s.c. and i.v.) will be pooled together.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand, including the primary endpoint, is defined in Section 2.1. It is based on the IGA response at week 16.

12.4.2 Statistical model, hypothesis, and method of analysis

The IGA data will be listed and summarized by treatment group. Placebo groups will be pooled. Summary tables will be presented by treatment group and visit which include absolute and relative frequencies.

12.4.3 Handling of remaining intercurrent events of primary estimand

Use of any therapy (prohibited or rescue medication taken after the first 6 weeks) as well as any study treatment discontinuation due to lack of efficacy or due to an AE related to AD are considered as unfavorable outcomes, and therefore the participants will be treated as non-responders (composite strategy). Study treatment discontinuation due to other reasons and AEs not related to AD or due to lack of tolerability will be handled with a treatment policy strategy (i.e. they will be ignored).

12.4.4 Handling of missing values not related to intercurrent event

Missing data imputations will be discussed in the Statistical Analysis Plan (SAP) in detail.

12.5 Analysis of secondary endpoints/estimands

Assessing safety and tolerability of CMK389 in participants with AD is the secondary CCI objective of the study.

12.5.1 Safety endpoints

For all safety analyses, the safety set will be used. All tables, figures and listings tables will be presented by treatment group and pooled placebo group (placebo s.c. and placebo i.v.).

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided, if there were death during the study. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 112 days after the date of the last actual administration of any study treatment.

Adverse events

All information obtained on adverse events will be displayed by treatment group (CMK389 10 mg/kg i.v, Placebo i.v, CMK389 300 mg s.c, Placebo s.c, and Pooled placebo) and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, and other significant adverse events leading to discontinuation.

The number (and proportion) of participants with adverse events of special interest (i.e. hypersensitivity reactions such as serum sickness and anaphylaxis) will be summarized.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The study is powered for the comparison between CMK389 10mg/kg i.v. vs placebo where both groups of placebo i.v. and placebo s.c. will be pooled together. The additional treatment group of CMK389 300mg s.c. will not be statistically tested against placebo.

CCI illustrates the operating characteristics for the design with 32 participants randomized to CMK389 10mg/kg i.v. and 16 participants on placebo.

The MAP prior for the placebo group is included in the analysis. Assuming the true treatment difference in IGA rate is 36% between CMK389 10mg/kg i.v. and placebo and assuming that the true placebo IGA rate is 7%, the probability of meeting the dual efficacy criteria as stated in Section 12.4.2 is 80%.

12.8.2 Secondary endpoint(s)

Not applicable.

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 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, written ICF, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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 protocol will be registered in a publicly accessible database such as EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and 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. EudraCT etc.)

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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 participants 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 prohibition, 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 participant 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 participant 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.

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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 Section 16.2 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 & follow-up requirements

Table 16-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 16-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
ALT or AST elevation with coagulopathy	
ALT or AST elevation accompanied by symptoms	
Isolated ALT or AST elevation > 8 × ULN	
Jaundice	
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the CRF Completion Guidelines.

Table 16-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase 50 % [+] OR if <18 years old, eGFR 35 mL/min/1.73 m^2	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3^+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3^+ on urine dipstick	• Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology. *(Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)*

- Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:
- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-5 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS
• Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) 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. • Analysis of urine markers in samples collected over the course of the DIN event