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Official Title:	A randomized, placebo-controlled, double-blind, parallel-group, multicenter Phase 2a study to investigate efficacy and safety of zabedosertib (BAY 1834845) for the treatment of adult patients with moderate-to-severe atopic dermatitis
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Title Page

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A randomized, placebo-controlled, double-blind, parallel-group, multicenter Phase 2a study to investigate efficacy and safety of zabedosertib (BAY 1834845) for the treatment of adult patients with moderate-to-severe atopic dermatitis

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Compound Number:	Zabedosertib (BAY 1834845)
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Study Phase:	2a
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Sponsor Name:	Bayer AG

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Protocol Date: **18 JUL 2023**

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This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the TMF and available on request.

Medical Monitor name and contact information will be provided separately.

Document History Table

DOCUMENT HISTORY			
Document	**Version**	**Date**	**Comments (if applicable)**
Amendment 1	2.0	18 JUL 2023	Global amendment that includes changes applicable to all countries
FRA-1	FRA-1	15 FEB 2023	To include changes specific for France (request from local ethics committee [EC])
Clinical Study Protocol	1.0	08 JUL 2022	

Protocol Amendment Summary of Changes

Amendment 1 (18 JUL 2023)

This amendment/modification is considered to be non-substantial based on the relevant criteria of the European Union clinical trial legislation.

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
9.4 Interim Analysis	Text added to describe the possibility of conducting an interim analysis during the ongoing study. Original text of this section ("No formal interim analysis using unblinded data is planned for this study, due to the short study duration" deleted.	Depending on recruitment progress, an interim analysis may be performed using the data of all study participants having either regularly completed or prematurely discontinued study intervention at a certain cutoff date, when a minimum of 80% of patients are evaluable. The further study conduct or study design will not be affected by the results of the interim analysis.
Throughout the document	Minor mainly editoral clarifications	

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List of Abbreviations

AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
BM	biomarker
BMI	body mass index
BSA	body surface area
CAD	canine atopic dermatitis
CAIA	collagen antibody-induced arthritis
CCl17/18	chemokine (C-C motif) chemokine ligand 17 and 18
CI	confidence interval
CK	creatine kinase
ClinRO	clinician-reported outcome
COVID-19	corona virus disease 2019
(e)CRF	(electronic) case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for AEs
CV	coefficient of variation
EASI	Eczema Area and Severity Index
EASI x response	x% reduction from baseline in the EASI, e.g. EASI 75 response
ECG	electrocardiogram or electrocardiography
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
ePRO	electronic patient-reported outcome
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
FiM	First-in-Man
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin

HCV	hepatitis C virus
HDL	high-density lipoprotein
HRQoL	health-related quality of life
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
hsCRP	high sensitivity C-reactive protein
IB	investigator's brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	independent ethics committee
Ig	immunoglobulin
IL	interleukin
IMQ	imiquimod
INR	international normalized ratio
LPS	lipopolysaccharide
IRAK4	interleukin1 receptor-associated kinase 4
IRB	institutional review board
IUD	intrauterine device
IRT	Interactive Response Technology
JAK	Janus kinase
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
M&S	Modelling and Simulation
MCP mod	Multiple Comparisons Procedure combined with modeling
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MTX	methotrexate
NRS	numerical rating scale
NYHA	New York Heart Association
OATP	organic-anion-transporting polypeptides
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PE	physical examination
PG	pharmacogenetic(s)
PID	participant identification
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
popPK	population pharmacokinetics
PPS	per protocol set
PT	preferred term
Q4	fourth quarter
QC	quality control
QD	once daily
q.i.d.	4 times daily

QoL	quality of life
R	software environment for statistical computing and graphics
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAS	Statistical Analysis System
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SoC	standard-of-care
SOC	System Organ Class
SOP	standard operating procedure
TB	tuberculosis
TBL	total bilirubin
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
TEAE(s)	treatment-emergent adverse event(s)
TEAESI	treatment-emergent adverse events of special interest
TESAE	treatment-emergent serious adverse event
TLR	toll like receptor
TSH	thyroid stimulating hormone
TSLP	thymic stromal lymphopoietin
ULN	upper limit of normal
vIGA-AD	validated Investigator Global Assessment for Atopic Dermatitis
vIGA-AD response	vIGA-AD of 0 or 1 with at least a 2-grade reduction from baseline
VRS	verbal rating scale
WBC	white blood cell
WOCBP	women of child-bearing potential

1 Protocol summary

1.1 Synopsis

Protocol Title:

A randomized, placebo-controlled, double-blind, parallel-group, multicenter Phase 2a study to investigate efficacy and safety of zabedosertib (BAY 1834845) for the treatment of adult patients with moderate-to-severe atopic dermatitis

Short Title:

Proof-of-concept of efficacy and safety of zabedosertib in the treatment of moderate-to-severe atopic dermatitis in adults

Regulatory Agency Identifier Number(s):

EudraCT Number: 2022-000520-38

Envisaged indication:

Moderate-to-severe atopic dermatitis in adults

Rationale:

Based on scientific considerations and preclinical observations, zabedosertib may provide a safe and effective treatment option for atopic dermatitis (AD) by its anti-inflammatory properties.

The aim of this Phase 2a study is to explore for the first time whether the interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor zabedosertib can safely provide a therapeutic benefit in patients with moderate-to-severe AD and to achieve a proof of concept for further development steps of the compound (or the compound class).

Objectives, Endpoints and/or Estimands:

Objectives	Endpoints
Primary objectives • To assess the efficacy of zabedosertib vs. placebo in adult patients with moderate-to-severe atopic dermatitis (AD) with inadequate response to topical corticosteroids or if topical treatments are medically not advisable	Primary endpoint: • Achievement of 75% reduction from baseline in the Eczema Area and Severity Index (EASI 75 response) at Week 12 (Day 84) Primary endpoint is the composite variable defined as follows: • an EASI 75 response at Week 12 (Day 84), • no stop of study intervention for reasons related to lack of efficacy, • no rescue medication use during the 4 weeks before Day 84 and • no use of systemic AD treatment Secondary endpoints: • Percent change from baseline in EASI at Week 12 (Day 84) • Achievement of EASI 50 response at Week 12 (Day 84) • Achievement of EASI 90 response at Week 12 (Day 84) • Achievement of a vIGA-AD response (score 0 or 1 and ≥ 2 points improvement) at Week 12 (Day 84) • Absolute change from baseline in body surface area (BSA) affected by AD at Week 12 (Day 84) • Absolute values and percent change of weekly average of the Peak Pruritus 0-10 NRS score from baseline at Week 12 (Day 84) • Achievement of a ≥ 4 point-improvement (reduction) in the weekly average of the Peak Pruritus 0-10 NRS score from baseline to Week 12 (Day 84) for participants with Peak Pruritus 0-10 NRS score ≥ 4 at baseline
Secondary objectives • To assess the safety and tolerability of zabedosertib vs. placebo	Secondary endpoints: • Frequency and severity of treatment-emergent adverse events (TEAEs) Other safety endpoints: • Frequency and severity of TEAEs of special interest • Changes in vital signs from baseline • Changes in clinical laboratory test results from baseline (e.g., chemistry, lipid panel, hematology, urinalyses) • Changes in electrocardiogram (ECG) parameters from baseline and frequency of ECG findings

Exploratory objectives and other pre-specified endpoints are listed in Section 3.

Overall Design Synopsis:

Disclosure Statement: This is a randomized, placebo-controlled, double-blind, parallel-group multicenter, Phase 2a study to investigate efficacy and safety of zabedosertib for the treatment of adult patients with moderate-to-severe atopic dermatitis.

Short Summary

The purpose of this study is to assess the efficacy and safety of zabedosertib compared with placebo in participants with moderate-to-severe AD. The study consists of an up to 28-day screening period (Visits 1 and 2), a 12-week intervention period consisting of 5 visits (Visits 3 to 7), and a 4-week follow-up (FU) period with one visit (Visit 8).

A total of 72 participants are planned to be randomly allocated to 1 of the 2 treatment groups with a 2:1 allocation ratio to achieve a total of 57 participants valid for efficacy analysis:

Zabedosertib at a dose of 120 mg BID:	48 randomized / 38 valid for the efficacy analysis
Matching placebo BID:	24 randomized / 19 valid for the efficacy analysis.

Efficacy parameters will be assessed prior to study intervention, during the 12-week intervention period and at follow-up according the Schedule of Activities (SoA).

All participants will be closely monitored for safety throughout the study.

To gain most accurate dosing data and to ensure adherence to study intervention, the data of participant's daily intake of study intervention will be collected as daily questions on an electronic patient handheld device. Participants are required to use additive-free emollients twice a day throughout the study. Participants will be reminded once a week about this requirement by the electronic hand held device.

Blood sampling for pharmacokinetic and pharmacodynamic evaluations will be obtained in accordance with the SoA.

At selected study sites in a subset of participants, skin biopsy samples will be taken for the assessment of gene expression and immunohistochemistry as indicated in the SoA.

Number of Participants:

Approximately 72 participants will be randomly assigned to the study to obtain 57 evaluable participants overall (2:1 randomization zabedosertib versus placebo).

Study Arms and Duration:

The total study duration per participant will be 17 to 20 weeks (approximately 140 days), with 8 study visits at intervals of 8 to 28 days with 2 study arms:

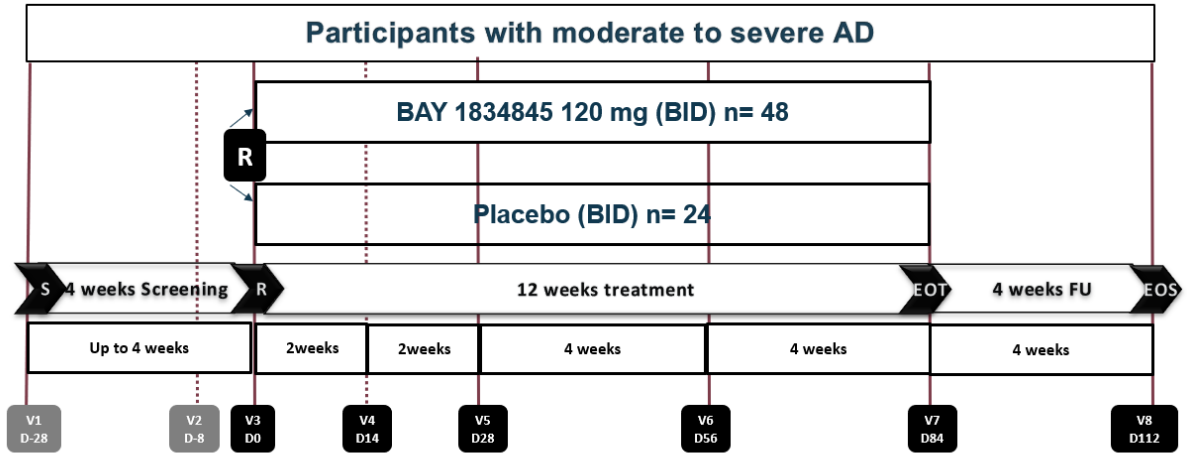
Zabedosertib at a dose of 120 mg BID orally:	48 randomized participants
Matching placebo BID orally:	24 randomized participants.

Dose changes and/or adjustments are not planned. Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Data Monitoring/Other Committee: No

1.2 Schema

Figure 1–1: Detailed schema



S= screening, R= randomization, V= visit, D= day, EOT= end of treatment, EOS= end of study

1.3 Schedule of activities (SoA)

	(For footnotes, see next page.)	Screening		Intervention period					Follow-up
				Randomization				EOT[1]	*Days after last dose* *28*[2]
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 (EOS)**
	Day	-28 to -14	-8 +1	1	14 ±2	28 ±2	56 ±3	84 ±3	112 ±3
Initiation	General Informed Consent	●							
	Consent Skin Biopsy[3]	●							
	Consent Photography[3]	●							
	Demography	●							
	Quantiferon TB Gold Plus test	●							
	HIV, hepatitis B and C	●							
	SARS-CoV-2 RNA test[4]		●						
	Medical history / history of AD	●							
	Prior medication / prior AD therapy	●		●					
	Height	●							
	Weight	●		●	●	●	●	●	●
	Check of in-/exclusion criteria	●	●	●					
Medication	Randomization			●					
	IRT registration	●		●	●	●	●	●	
	Study intervention dispensation			●	●	●	●		
	Study int. return / accountability				●	●	●	●	
	Study intervention intake			[0]←——— ongoing ——→					
	Enter intervention intake into eDiary			←——— ongoing ——→					
	Concomitant medication	●	●	●	●	●	●	●	●
Efficacy	**ClinROs**								
	- EASI	●		●	●	●	●	●	●
	- vIGA-AD	●		●	●	●	●	●	●
	- BSA affected by AD	●		●	●	●	●	●	●
	ePRO								
	- Dispense and training of patient handheld device		●						
	- Daily Peak Pruritus 0-10 NRS[6]	←——— ongoing ——→							
	- Return handheld device								●
	Other procedure: photograph[0]			●				●	●
Safety	Complete physical examination	●		●				●	●
	Symptom-directed PE/inspection		●		●	●	●		
	AE/SAE assessment	●[8]	●[8]	●	●	●	●	●	●
	AESI assessment	●[8]	●[8]	●	●	●	●	●	●
	Pregnancy test – S(erum) / U(rine)	●S	●S	●U	●U	●U	●U	●U	●S
	Safety panel (central lab)[9]	●	●[10]	●	●	●	●	●	●
	Lipid profile (central lab)			●				●	
	Urinalysis	●	●[10]	●		●		●	●
	12-lead ECG[11]	●			●			●	●
	Vital signs	●	●	●	●	●	●	●	●
PK/PD	BM blood samples[12]			●				●	
	BM on-study skin biopsy [13,14]			●				●	
	PK blood sample			●[15]	●[16]	●[16]	●[16]	●[15,16]	

Footnotes for schedule of activities (see next page)

Footnotes for schedule of activities

AD = atopic dermatitis; AE(SI) = adverse event (of special interest); BM = biomarker; BSA = body surface area; ClinROs = clinician-reported outcomes; CRP = C-reactive protein; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; eDiary = electronic diary (= patient handheld device); EOS = end of study; EOT = end of treatment; HIV = human immunodeficiency virus; IRT = Interactive Response Technology; NRS = numerical rating scale; PD = pharmacodynamc(s); PE = physical examination; PK = pharmacokinetic(s); PRO = patient-reported outcome; RNA = ribonucleic acid; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; v = visit; vIGA-AD = validated Investigator's Global Assessment for Atopic Dermatitis

Early Discontinuation: Visit 7 (EOT) and Visit 8 (EOS) assessments should be performed

Performed 28 days after last dose of study intervention

Optional, should be obtained for participants taking part in the skin biopsy subgroup or the photograph subgroup. Consent can be obtained up to Visit 3.

In exceptional cases, e.g., if test results are not available in time, SARS-CoV-2 test (PCR test or similar test) may be performed locally.

First dose of study intervention should only be taken after all baseline assessments are completed.

Daily assessment should start 7 days before randomization visit.

At select study sites (optional): Photographs of a representative area of AD involvement (e.g., the lesioned area used for EASI assessments). Instructions for taking the photographs will be provided in a photography manual.

Only (S)AEs which are related to protocol-required study procedures should be recorded before start of study intervention (all other events should be recorded as medical history).

Safety panel (central lab) will include parameters listed in Appendix 10.2 (Table 10-1)

Only CRP, blood count, and urinalysis must be re-assessed at Visit 2 to rule out asymptomatic infections; further lab values only in case results from screening lab (Visit 1) require re-testing for eligibility or clinically indicated control-analyses.

May be performed + 3 days of visit. All ECG reports are to be assessed for clinical significance by a physician.

Blood samples (plasma and whole blood) for molecular biomarkers (optional analysis)
In total 2, BM samples will be collected: 1x biomarker blood plasma and 1x biomarker whole blood. See Table 8–1 for further details to BM samples.

At select study sites (optional): Skin lesion biopsy samples (2 x 3 mm punch biopsies per timepoint) in approximately 40 participants for assessment of gene expression (e.g., inflammation and skin barrier markers) and immunohistochemistry (e.g., immune cells; optional analysis).
Two BM samples each at baseline and at EOT will be collected: biomarker on-study skin biopsy for mRNA expression and 1x biomarker on-study skin biopsy for IHC expression. See Table 8–1 for further details to BM samples.

Optional procedure requiring a separate informed consent

Post-morning dose blood samples for pharmacokinetics between 0.5 to 1.5 hours post-dose, and between 2 to 5 hours post-dose with at least 1 hour difference between the 2 post-dose samples. NOTE: At visits with PK, study drug intake of the morning dose should occur at the study site. The participants should bring their handheld devices to these visits as well.

Blood samples for pharmacokinetics should be taken pre-dose. NOTE: At visits with PK, study drug intake of the morning dose should be taken at site. The participants should bring their handheld devices to these visits as well.

2 Introduction

2.1 Study Rationale

Despite the abundance of topical and systemic therapeutic options, disease management in patients with moderate to severe AD is often difficult. The available drugs have either unsatisfactory efficacy, require parenteral application or their safety profile contains an increased risk for significant adverse events. Based on scientific considerations and preclinical observations, zabedosertib may offer a new treatment option for patients suffering from moderate to severe AD and inadequately responding to topical therapy due to its anti-inflammatory properties.

The aim of this Phase 2a study is to explore whether the IRAK4 inhibitor zabedosertib can safely provide a therapeutic benefit in patients with moderate-to-severe AD and to achieve a proof of concept for further development steps of the compound.

2.2 Background

2.2.1 Disease Background

AD, also known as atopic eczema, is a common, chronic and relapsing inflammatory skin disorder with increasing incidence especially in developed countries. The adult prevalence of AD varies in published literature between 2.1% in Japan, 3.5% in Canada, 4.9% in the US and in the EU with individual ranges of 2.2% for Germany to 8.1% for Italy (Barbarot et al, 2018). The prevalence generally is lower for males compared to females and decreases with age. AD causes high health-care costs and has become a global health issue with considerable morbidity and quality of life (QoL) impairment with limited treatment options for moderate-to-severe AD (Silverberg et al, 2017). AD is often the first step in the development of other atopic diseases such as allergic rhinitis, allergic asthma and food allergy, the so-called atopic march.

AD is characterized by a chronic or relapsing course with acute flares of eczematous pruritic lesions over dry skin, with the tendency to bacterial superinfections, lichenification and prurigo nodules. Itch may cause mental symptoms (Patel et al, 2019), and, if experienced at night may result in sleep disturbances with the result of daytime fatigue, irritability, decreased motor performance and negative impact on health-related quality of life (HRQoL) (Bawany et al, 2021). There is no specific test or biomarker (BM) for AD, however, the most typical laboratory parameter is the elevation of total or allergen-specific IgE levels in serum (Torres et al, 2019).

2.2.2 Current Treatment Options and Unmet Medical Need

AD is currently managed with topical and systemic treatments, as well as phototherapy. For mild and moderate AD topical therapy is mainly the most frequent option: emollients / moisturizers as background therapy promote the hydration of the skin by at least twice daily application and topical corticosteroids (TCS) are a first-line anti-inflammatory treatment, applied on inflammatory skin according to the needs (pruritus, sleeplessness, new flare). Topical calcineurin inhibitors (TCI) are effective for acute and chronic treatment, especially in selected anatomical areas (Wollenberg et al, 2018).

Although mild and moderate AD may be managed appropriately with TCSs, TCIs and/or phototherapy, a considerable part of patients with AD requires systemic treatments to allow for adequate symptom control (Suga H, Sato S. 2019). Conventionally, the main systemic

treatment for AD has been cyclosporine; however, relapse is frequently seen soon after treatment withdrawal. Moreover, nephrotoxicity and hypertension are the most significant side effects of cyclosporine limiting long term use and usability for some patient populations. Although other immunosuppressive drugs, such as methotrexate and azathioprine, have also been used to treat severe AD, methotrexate's exact mechanism of action in inflammatory diseases, including AD, is not fully understood and azathioprine can cause myelosuppression and carries an increased risk of infection, lymphoma and non-melanoma skin cancers (Wollenberg et al, 2018).

Dupilumab, a fully human monoclonal antibody that blocks the common α-chain of the receptor for interleukin-4 and interleukin-13, modulating both the interleukin-4 and interleukin-13 pathways, has been approved alone or in combination with TCSs by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA) as a first-line biologic treatment for moderate-to-severe AD. Limited efficacy and side effects such as conjunctivitis as well as the parenteral route of administration limit its use in AD.

In 2020, the first in-class oral selective Janus kinase (JAK) inhibitor, baricitinib, was approved in the EU and in Japan. This was followed by approvals of other oral, selective and reversible JAK inhibitors, upadacitinib and abrocitinib by EMA and FDA by the end of 2021 and January 2022 for patients with moderate to severe AD.

For mild to moderate AD, ruxolitinib cream was approved by the FDA in September 2021. All JAK inhibitors have a rapid onset of action and were shown to be at least as efficient as dupilumab (Papp et al, May 2021; Bieber et al, June 2021). However, they potentially increase the risk of serious infections, non-melanoma skin cancer and thromboembolism (Reich et al, 2020; Silverberg et al, 2020; Simpson et al, 2020). Moreover, the need for continuous blood monitoring, possible pre-vaccination for herpes zoster in susceptible patients and drug to drug interactions might restrict their use to some patients (Thyssen & Thomson, 2021). In addition, a safety review of JAK inhibitors in the treatment of inflammatory disorders has been initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004 in February 2022.

In 2021 tralokinumab, a monoclonal Interleukin (IL)-13 antibody was approved by EMA, MHRA and FDA for patients with moderate to severe AD who are candidates for systemic therapy. Although, vIGA-AD and EASI response rates were lower compared to dupilumab at Week 16, as an advantage over dupilumab approximately 50% of the tralokinumab responders did not need any rescue medication including topical steroids up to Week 52 (Wollenberg et al, 2021, Silverberg et al, 2021).

Other biologics targeting IL-13 such as lebrikizumab and the IL-31 receptor anatagonist nemolizumab are in an advanced stage of drug development (Guttman-Yasky et al, 2020; Silverberg et al, 2020). However, their parenteral application with potential injection site reaction as well as increased occurrence of upper respiratory tract infections and conjunctivitis may limit their use.

Despite the mentioned therapeutic options, the treatment of moderate-to-severe AD remains challenging and novel, efficacious, safe and targeted treatment alternatives are urgently needed (Hon et al, 2020).

2.2.3 Rationale for IRAK4 inhibitors as an AD treatment option

IRAK4, is the key isoform of a 4-kinase family regulating the production of proinflammatory cytokines. IRAK4 is the first of the 4 kinases mediating the intracellular signal transduction pathway utilized by the innate immune cell receptors e.g., IL-1R, IL-18 receptor (IL-18R), IL-33 receptor (IL-33R) and Toll-like receptors (TLRs) except TLR3.

When these receptors are bound with multiple exogenous ligands, endogenous stimuli or proinflammatory cytokines, they initiate the first wave of inflammatory signals and innate immune responses propagating and amplifying these signals. These receptors are constitutionally expressed on a variety of innate immune cells and other cell types including macrophages, fibroblasts, monocytes and endothelial cells. The role of IRAK4 as a key component of Toll/Interleukin-1 receptor signaling and potential inhibition being associated with a low rate of infectious complications (Wiese et al, 2020) constitutes a promising therapeutic option in AD management.

Based on the following observations, theoretical considerations and scientific knowledge, there is good scientific rationale to assume positive effects on AD by inhibition of the IRAK4 enzyme:

- Genetic loci associated with the susceptibility to develop AD encompasses components of the IRAK4 signaling including IL1β and IL-18 receptor (Dainichi et al, 2018).
- Epidermal barrier disruption is one of the key mechanism promoting inflammation in AD that is associated with members of the IL-1R family (e.g., IL-1β and IL-33) (Weidinger et al, 2018).
- Specific overexpression of IL-18 in the skin leads to the spontaneous development of AD-like inflammatory skin lesion in a murine animal model (Konishi et al, 2002).
- The lack of components of the IRAK4 pathway like MyD88 (Myeloid differentiation primary response 88, component of the IRAK4 signaling complex), IL-1 and IL-33 improves characteristic of AD in different murine disease models (Didovic et al, 2016; Imai et al, 2019; Li et al, 2017; Sun et al, 2019).
- Reduction in skin lesions (CADESI) and pruritus achieved after 28 days of treatment with BAY 1834845 (an IRAK4 inhibitor with comparable potency) in 2 pilot field studies in privately owned dogs (treating > 70 dogs in total) with canine atopic dermatitis (CAD) (data on file).

2.2.4 Zabedosertib (BAY 1834845)

BAY 1834845 is a potent and highly selective interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor and provides a new approach for the treatment of AD and other inflammatory diseases such as rheumatoid arthritis. IRAK4 is a pro-inflammatory kinase that is essential for nuclear factor-κB (NF-kB) and mitogen-activated protein kinase (MAPK) activation in toll like receptor (TLR, except TLR3) and interleukin-1 receptor (IL-1R, including IL-1, IL-18 and IL-33) family-driven processes leading to inflammatory skin lesions. IRAK4 induces the production and activation of a variety of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF α), interleukin-1 beta (IL-1β), IL-6, interferon gamma (IFN-γ) and IL-17, all cytokines that play a critical role in various inflammatory conditions.

Further information can be found in the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

Emerging safety issues which affect the benefit/risk assessment of the study will be communicated as soon as possible between the sponsor, all study sites and investigators, trial participants, health authorities and ethics committees.

This Benefit-Risk-Assessment takes into account safety information from the development compound zabedosertib and a competitor IRAK4 inhibitor program (development candidate PF-06650833 for RA and emavusertib (GS-5718) for cancer).

More detailed information about the known and expected benefits and risks of BAY 1834845 can be found in the Section 5.3 of the IB.

2.3.1 Risk Assessment

Risks in relation to pharmacological IRAK4 inhibition

It is known that IRAK4-deficient persons are prone to pyogenic infections in childhood, a risk which vanishes after maturation of the adaptive immune system during puberty. However, to reduce the risk for the adult study population participants with scheduled (elective) surgery, planned hospitalization or dental treatment will be excluded from participation in this Phase 2a study to avoid an iatrogenic bacteremia that could pose a potential risk for infection.

Additionally, during the study, participants will be carefully examined regarding early signs of infectious diseases during the study visits, measurement of vital signs and inflammatory parameters such as C-reactive protein. All confirmed severe invasive bacterial infections, systemic hypersensitivity reactions and non-invasive infections (skin) will be required to be reported as adverse events of special interest.

Information related to zabedosertib

CCI

CCI [redacted]

In addition, a mechanistic study (#21329) in healthy volunteers was conducted with a topically applied TLR7/8 activator (imiquimod = Aldara cream) as well as in a systemic challenge with intravenous lipopolysaccharides (LPS). Topline results of the mechanistic study with zabedosertib (BAY 1834845 120 mg BID for 7 days, N=12) showed that the IRAK4 inhibitor had a distinct and significant effect over placebo in the skin (i.e., alleviation erythema) as well as systemically, assessed by significant reduction in pro-inflammatory cytokines. PK concentrations of zabedosertib in skin suction blisters as a surrogate for skin exposure showed approx. 50% of plasma concentration. No safety concerns were observed during the study (data on file).

For further details refer to the IB.

CCI [redacted]

For further details refer to the IB.

Table 2–1: Risk overview

Potential risk of clinical significance	Summary of data / rationale for risk	Mitigation strategy
	Study intervention	
Infections	Based on the mode of action, therapeutic inhibition of IRAK4 may result in a modified innate immune response to infections. Clinical effects of IRAK4 inhibition may therefore, in theory, include increased susceptibility or modified course of infections. Congenital IRAK4 deficiency is associated with pyogenic infections caused by Staphylococcus aureus, and Pseudomonas aeruginosa, but not from other bacterial, fungal, or viral infections that have been reported to require TLR/ IRAK-4 signaling in animal experimental models (Picard C et al 2003). Current preclinical and clinical data with zabedosertib and other compounds inhibiting IRAK4 currently do not indicate an increased infection risk by the pharmacological inhibition of IRAK4. The effect of Zabedosertib on immune function (potential susceptibility to infections) is regarded to be of low relevance in immunocompetent participants within this study due to the limited inhibition of the IRAK4 pathway-related signaling by zabedosertib.	• Exclusion of patients with active, latent, chronic, recurrent infections (see Exclusion criteria #2) • Only immunocompetent participants will be enrolled in the study. • Regular clinical examination and laboratory assessment of infections • Reporting of infections (AEs/SAEs, TEAEs, AESIs) • Only SARS-CoV-2-virus-RNA-test-negative participants without any symptoms of COVID-19 prior to randomization to treatment. As part of the clinical study procedures, participants will be closely monitored for signs symptoms of COVID-19 during the entire study duration. Study intervention will be terminated for all study participants with a SARS-CoV-2 positive test result. During the entire study, all recommendations issued by the health authorities as well as local guidelines with respect to minimizing the risk of disease spreading, e.g., social distancing, disinfection, hygiene, and wearing of mouth-nose masks need to be followed and further measures according to recommendations and requirements from local health authorities may become necessary and will be followed within the context of this study as far as applicable in order to ensure full implementation of the principles of GCP with priority on subject safety.
Embryotoxicity and teratogenicity	BAY 1834845 was embryotoxic and, at the highest tested dose, also teratogenic in the studies on embryofetal development in mice with safety margins of less than 1 when looking at total exposure. With regard to unbound exposure, the safety margin for teratogenicity was 10 to 14.	• Exclusion of pregnant women • Appropriate contraception measures for women of child-bearing potential (WOCBP) and study participants with WOCBP as partners are required. • Serum pregnancy test will be performed for WOCBP at screening Visit 1 and Visit 2 and at end of study visit (EOS, 28 days after the last drug dose intake). In addition, regular urine pregnancy tests will be carried out at randomization (Visit 3) and at Visit 4

Potential risk of clinical significance	Summary of data / rationale for risk	Mitigation strategy
		(Day 14), Visit 5 (Day 28), Visit 6 (Day 56) including the end-of-treatment visit (Day 84).
Rhabdomyolysis	In an ongoing clinical study in which a research molecule of the same drug class as BAY 1834845 was tested, a case of severe muscle damage (rhabdomyolysis) with lethal outcome was observed in a patient with a malignant disease.	Although this case refers to a different molecule and the relationship to the study drug is yet under investigation, some measures to identify any myopathies are implemented in this study: • Frequent testing of CK in serum • Discontinuation in case of elevated CK or suspicion of myopathy/rhabdomyolysis • Instruction of participants to abstain from intensive exercise and to report symptoms of myopathy (e.g., muscle weakness, muscle pain), change of color of urine or urinary retention • Guidance for management of muscle symptoms and CK increase • Unexplained cases of rhabdomyolysis defined as AESI.
	Study procedures	
Blood sampling (by single vein puncture and/or indwelling cannula) may be accompanied by mild pain, hematoma and in rare cases inflammation of the vessel wall or injury of a nerve.	This presents minimal risk as related documented AEs observed in prior studies are mild and were completely resolved.	All study assessments will be carried out by trained clinical staff.
Complications from skin biopsy	Participants who consent to participate in the skin biopsy substudy may experience minor complications such as pain, bleeding, bruising, and/or scarring from the skin biopsy, infection or damage of the structures in the vicinity of the biopsy site (e.g., vessels and skin nerves).	Only sites with experience in skin biopsy sample collection will participate in the skin biopsy substudy.
	Other	
Not applicable.	Not applicable.	Not applicable.

AE = adverse event; AESI = adverse event of special interest; CK = creatine kinase, COVID-19 = corona virus disease 2019; GCP = Good Clinical Practice; IRAK4 = interleukin1 receptor-associated kinase 4; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential

2.3.2 Benefit Assessment

Participation in this study with the administration of zabedosertib may be associated with the following benefits:

- Overall improvement of the skin condition, reduction of pruritus and improvement of AD-related symptoms and signs, e.g., pain, sleep disturbances with resulting positive impact on reduced HRQoL.
- Contributing to the process of developing new therapies in an area of unmet need.
- Close medical and treatment monitoring including regular investigations associated with study procedures (e.g., physical examinations, electrocardiogram (ECG), laboratory evaluations) can be regarded as beneficial.

In addition, the data obtained from this study in regard to safety, tolerability, and PK will form the basis for further development of zabedosertib in AD and other inflammatory conditions.

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with zabedosertib are acceptable by the anticipated benefits that may be afforded to participants with AD during the study, and the benefit for patients with AD by a potential continued development of zabedosertib in this indication.

3 Objectives, Endpoints, and Estimands

3.1 Objectives and Endpoints

Objectives	Endpoints
Primary objective • To assess the efficacy of zabedosertib vs. placebo in adult patients with moderate-to-severe atopic dermatitis (AD) with inadequate response to topical corticosteroids or if topical treatments are medically not advisable	Primary endpoint: • Achievement of 75% reduction from baseline in the Eczema Area and Severity Index (EASI 75 response) at Week 12 (Day 84) Primary endpoint (see Section 3.2) is the composite variable defined as follows: • an EASI 75 response at Week 12 (Day 84), • no stop of study intervention for reasons related to lack of efficacy, • no rescue medication use during the 4 weeks before Day 84 and • no use of systemic AD treatment.
	Secondary endpoints: • Percent change from baseline in EASI at Week 12 (Day 84) • Achievement of EASI 50 response at Week 12 (Day 84) • Achievement of EASI 90 response at Week 12 (Day 84) • Achievement of a vIGA-AD response (score 0 or 1 and ≥ 2 points improvement) at Week 12 (Day 84) • Absolute change from baseline in body surface area (BSA) affected by AD at Week 12 (Day 84) • Absolute values and percent change of the weekly average of the Peak Pruritus 0-10 NRS score from baseline at Week 12 (Day 84) • Achievement of a ≥ 4 point-improvement (reduction) in the weekly average of the Peak Pruritus 0-10 NRS score from baseline at Week 12 (Day 84) for participants with Peak Pruritus 0-10 NRS score ≥ 4 at baseline

Objectives	Endpoints
Secondary objectives	
• To assess the safety and tolerability of zabedosertib vs. placebo	Secondary endpoints: • Frequency and severity of TEAEs Other safety endpoints: • Frequency and severity of TEAEs of special interest • Changes in vital signs from baseline • Changes in clinical laboratory test results from baseline (e.g., chemistry lipid panel, hematology, urinalyses) • Changes in ECG parameters from baseline and frequency of ECG findings
Other pre-specified / Exploratory objectives	Other Pre-Specified Endpoints
• To further assess the efficacy of zabedosertib vs. placebo	• Achievement of EASI 75 response up to Week 8 (Day 56) • Achievement of EASI 100 response at Week 12 (Day 84) • Achievement of a ≥ 3 point- improvement (reduction) in the weekly average of the Peak Pruritus 0-10 NRS from baseline at Week 12 (Day 84) • Absolute values and percent change from baseline in weekly averages of Peak Pruritus 0-10 NRS scores over time
• Exploration of the pharmacokinetics of zabedosertib	• Plasma concentrations of zabedosertib and metabolite BAY 28822815 (M-5) and population pharmacokinetic (popPK) evaluation derived PK parameters (will be reported separately, if applicable)
• Pharmacodynamics disease-monitoring biomarkers by:	
• Assessment of treatment response by analysis of blood biomarkers (BM)	• Plasma levels of inflammatory markers (optional analysis)
• Evaluation of skin biopsies (subset of participants)	• Measurement of molecular changes in AD transcriptome reg. inflammatory cytokines, chemokines (e.g., IL-1β, IL-4, IL-33, TSLP) and immunohistochemistry (e.g., epidermal barrier markers; optional analysis).

3.2 Estimand

The estimand for the primary endpoint is shown below.

Primary Objective: See Section 3.1
Estimand label: primary
Endpoint: Achievement of 75% reduction from baseline in the Eczema Area and Severity Index (EASI) at Week 12 (Day 84) – EASI 75 response
Population: Adult patients with moderate-to-severe atopic dermatitis (for at least one year and inadequate response to topical treatment or if topical treatments are medically not advisable)
Treatment condition: Zabedosertib vs placebo
Population-level summary: The estimated difference in the proportion of responders between interventions.

Intercurrent event(s)

- Use of topical rescue medication:
  At Day 56 (Visit 6) or later:
  analyze study participant as non-responder (composite strategy)

  Before Day 56 (Visit 6):
  disregard use of topical rescue medication (treatment policy strategy)
- Use of systemic standard of care:
  analyze study participant as non-responder (composite strategy)
- Discontinuation of treatment due to lack of efficacy:
  analyze study participant as non-responder (composite strategy)
- Discontinuation of treatment due to reasons not related to lack of efficacy (including Covid-19 related reasons):
  At Day 56 (Visit 6) or later:
  imputation of response information (hypothetical strategy)

  Before Day 56 (Visit 6):
  exclusion from analysis as adequate imputation of response information is considered not possible
- Non-compliance with study intervention (general), defined as actual drug intake lower than 80% of the planned drug intake. Actual drug intake will be calculated from the date of first drug intake until end of treatment or start of rescue medication (at or after Day 56 (Visit 6)), whatever comes first:
  exclusion from analysis as adequate imputation of response information is considered not possible
- Non-compliance with study intervention (last 4 weeks) defined as actual drug intake lower than 80% of the planned drug intake during the last 4 weeks. Reference point for determination of the time period will be either the end of treatment or the start of rescue medication (at or after Day 56 (Visit 6)), whatever comes first.:
  exclusion from analysis as adequate imputation of response information is considered not possible
- Non-compliance with emollients / moisturizers:
  regardless of non-compliance with emollients / moisturizers (treatment policy)
- Missing baseline value EASI assessment:
  exclusion from analysis as adequate imputation of response information is considered not possible
- Missing Day 84 (Visit 7) EASI assessment:

  imputation of response information using data from Day 56 (Visit 6) or later (hypothetical strategy), if none of the conditions applies which are described above.
- Missing Day 56 (Visit 6) and later EASI assessment:
  exclusion from analysis unless participant is a non-responder due to use of rescue medication, SOC or treatment discontinuation due to lack of efficacy

4 Study Design

4.1 Overall Design

Study 22158 is a Phase 2a proof of concept (PoC) study.

Randomized, placebo-controlled, double-blind, 2-arm, parallel-group, multi-center Phase 2a study. The study consists of

- a 28-day screening period (Visits 1 and 2),
- a 12-week intervention period consisting of 5 visits (Visits 3, 4, 5, 6, and 7),
- and a 4-week follow-up (FU) period with one visit (Visit 8).

Thus, the total study duration per participant will be 17 to 20 weeks (approximately 140 days), with 8 study visits at intervals of 8 to 28 ± 3 days.

Screening period

During the screening period, potential study participants will be identified, and informed consent will be obtained prior to the initiation of any study-related procedures. Participants will then be evaluated for eligibility against the study-specific inclusion and exclusion criteria.

Emollients used by the participant before entering the study should be continued with the same frequency/intensity. At least 7 days before the randomization visit, participants are required to use a stable amount (i.e., approximately the same amount for each application) of topical drug-free emollient to moisturize the skin applied to the whole body twice a day, which should continue during the study.

During the same 7-day period, participants will daily record the intensity of their peak pruritus using a 0-10 numerical rating scale (NRS) [Peak Pruritus 0-10 NRS] displayed on the electronic patient handheld device.

Randomization

Randomization will be done at the randomization visit on Day 1, i.e. at the end of the screening period.

A total of 72 participants are planned to be randomly allocated to 1 of the 2 treatment groups with a 2:1 allocation ratio to achieve a total of 57 participants valid for efficacy analysis:

zabedosertib at a dose of 120 mg BID:	48 randomized / 38 valid for the efficacy analysis
Matching placebo BID:	24 randomized / 19 valid for the efficacy analysis.

Intervention period

During the intervention period, participants will take the study intervention twice daily. The participants will receive two tablets per day, one tablet of zabedosertib or placebo in the morning and in the evening.

Skin condition will be assessed regularly using validated ClinROs in AD, such as the Eczema Area and Severity Index (EASI), validated Investigator's Global Assessment scale for atopic dermatitis (vIGA-AD), and the assessment of the BSA affected by AD.

In addition, the patient-reported outcome Peak Pruritus 0-10 NRS will be used to investigate further efficacy of zabedosertib.

All participants will be closely monitored for safety throughout the study.

To gain most accurate dosing data and to ensure adherence to study intervention, the data of participant's daily intake of study intervention will be collected as daily questions on an electronic patient handheld device.

Blood sampling for pharmacokinetic and pharmacodynamic evaluations will be done in all participants.

At selected study sites in a subset of participants, skin biopsy samples will be taken for the assessment of gene expression and immunohistochemistry.

To control worsening of AD symptoms, topical rescue treatment is defined and may be provided to study participants at the discretion of the investigator, if required.

If additional systemic treatment for AD is initiated, the participant needs to stop the study treatment and should undergo safety and efficacy assessments as scheduled for the end-of-treatment (EOT) visit and complete the FU visit.

Follow-up period

After the end of study intervention, participants will be followed up for safety and any changes in efficacy parameters for further 28 days.

4.2 Scientific Rationale for Study Design

This Phase 2a study protocol was designed to explore the effects of zabedosertib on moderate-to-severe AD.

A randomized, double-blind, placebo-controlled design is considered appropriate to assess the study objectives listed in Section 3 in the population of interest, which are adult patients with moderate-to-severe AD. The EASI was chosen as the primary endpoint measure and is a well-established and frequently used instrument in clinical studies to assess the severity and extent of AD.

An intervention duration of 12 weeks (84 days) is considered appropriate to observe efficacy in this study population and to investigate potential changes in safety parameters.

4.3 Participant Input into Design

Participant involvement in the design of the clinical study was collected via several structured feasibility processes interacting with study sites interested in taking part in the clinical study. AD patients were also consulted via 2 different methods:

- A sponsor internal patient questionnaire making use of the input of 114 individuals with AD (sponsor employees), (data on file).
- A patient advisory board conducted with AD patients, interviewed according to a questionnaire provided by the study team.

These consultations provided patients feedback about their disease, treatments and some of the study processes.

Processes were adapted whenever it was possible where concerns were identified during the feasibility with sites and through patient's consultations.

4.4 Justification of Dose

This study aims to generate first evidence of efficacy of the IRAK inhibitor zabedosertib in AD. Specifically, this study assesses whether, and if so, to what extent treatment with zabedosertib is associated with a reduction of AD symptoms in adult patients suffering from moderate-to-severe AD over a timeframe of 12 weeks. Based on its mode of action and preclinical information, IRAK4 inhibition is expected to reduce skin inflammation and pruritus in patients with AD. In addition, a mechanistic study (21329) to assess the pharmacological activity of oral administrations of zabedosertib on the inhibition of IRAK4 pathway mediated reactions upon local and systemic challenges is operationally completed and data showed a positive and promising outcome.

The dose was selected because the results from Phase 1-Studies 18384 and 18385 demonstrate that plasma concentrations achieved with 120 mg BID are expected to reach the anticipated therapeutic exposure levels (see below) and a higher dose resulted in only slight respectively no increase in exposure (a dose of 200 mg BID was tested in Study 18385 (part 1, healthy volunteers) and was safe and well tolerated but resulted in no exposure increase). Also, this dose is considered well suited since single doses up to 480 mg zabedosertib were well tolerated by healthy male participants in Study 18384. Similarly, results from Study 18385 (part 2, patients with psoriasis) showed acceptable tolerability of 120 mg zabedosertib BID for 8 weeks. For details please refer to IB zabedosertib.

The estimated human efficacious exposure for the indication rheumatoid arthritis was based on experimental data from a mouse collagen antibody-induced arthritis (CAIA) model in female Balb/C mice. The unbound AUC (AUC_u) to achieve 50% efficacy was determined as 20 mg h/L. Due to species differences in potency between mouse and human, this translates to an AUC_u in human of 4.7 mg h/L, which was considered as therapeutic human AUC_u. The dose of 120 mg BID in humans resulted in a coverage of 136% of the estimated human efficacious exposure.

Also, clear evidence for pharmacological activity of the dose of 120 mg BID in the skin and systemically was demonstrated in the Mechanistic Study 21329 in a human imiquimod skin challenge model and in a systemic LPS challenge (data on file) suggesting efficacy in AD. Relevant concentrations of zabedosertib were further detected in skin suction blisters, indicating a skin exposure of about 43% in relation to the systemic exposure.

12 weeks are considered to be adequate to show an effect in this patient population and to assess safety and tolerability in patients with AD to decide on the further development in this indication as well as to benchmark against other development drugs.

Only one active dose is used in this study to limit the number of participants who are exposed in reflection of the fact that there is no clinical experience with the IRAK inhibitor zabedosertib in patients suffering from AD.

No dose modification is intended in this study (see Section 6.6).

4.5 End of Study Definition

A study participant is considered to have completed the study, if the participant has completed all phases of the study including the FU visit.

The end of the study is defined as the date of the clean database.

Primary completion

The primary completion is defined as the date of the last treatment of the last participant.

5 Study Population

The study population consists of adult patients with a clinical diagnosis of AD for ≥ 1 year and moderate-to-severe disease intensity at study entry. For details of eligibility criteria see Section 5.1 and 5.2.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. 18 to 65 years of age inclusive, at the time of signing the informed consent.
2. Diagnosis of AD for ≥ 1 year at the screening visit.
3. Moderate-to-severe AD at randomization visit as defined by
   - EASI score ≥ 16,
   - BSA affected by AD ≥ 10%,
   - vIGA-AD score ≥ 3, and
   - Peak Pruritus 0-10 NRS ≥ 4 (average score of the daily scores of the 7 days before randomization, with ≥ 4 scores required).
4. Documented history (within 6 months prior to the first screening visit) of inadequate response to treatment with topical corticosteroids (TCS), or if TCS are medically not advisable (e.g., due to important side effects or safety risks).
   - Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to vIGA-AD 0 = clear to 2 = mild) in spite of treatment with a daily regimen of TCS of moderate or higher potency, see WHOCC, ATC/DDD Index as a guidance (± TCI as appropriate), applied for at least 28 days or for the maximum duration recommended if less than 28 days by the product prescribing information (e.g., 14 days for super-potent TCS), whichever is shorter.
   - Documented systemic treatment for AD in the past 6 months also qualifies as inadequate response to topical treatments.
   - Important side effects or safety risks are considered to be those risks that outweigh the potential treatment benefits. They include intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the patient's treating physician.
   - Acceptable documentation must be obtained, which includes concurrent chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician. If documentation is insufficient, potential patients may be re-screened after such documentation is obtained (i.e., patients are shown to fail a 28-day course of moderate or higher potency TCS).

5. Stable amount of emollient applied to skin over the whole body twice daily for at least the 7 consecutive days before the randomization visit (NOTE: further instructions regarding emollients / moisturizers can be found in Section 6.9.1).
6. Body mass index (BMI) within the range of 18.5 to 35.0 kg/m^2 (inclusive) at screening (Visit 1) and randomization visits.
7. Women of childbearing potential (WOCBP; for definition, see Section 10.4) and male subjects able to father children must agree to use adequate contraception when sexually active. This applies since the signing of the informed consent form until 30 days after the last study intervention administration. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   Male Participants:

   Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 30 days after the last dose of study intervention:

   - Must agree to use contraception / barrier as detailed below:
     - Agree to use a male condom with female partner use of an additional highly effective contraceptive method with a failure rate of < 1% per year as described in Appendix 4 Contraceptive and Barrier Requirements (see Section 10.4).

   or

   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
   - Refrain from donating sperm.

   Female Participants:

   - A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
     - Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4 (see Section 10.4). Contraception and Barrier Guidance.
     - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 4 (see Section 10.4). Contraception and Barrier Guidance during the study intervention period and for at least 30 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
   - A WOCBP must have a negative highly sensitive pregnancy test (urine) as required by local regulations within 24 hours before the first dose of study intervention, see Section 8.3.5 Pregnancy Testing.
     - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5 Pregnancy Testing.
- The investigator is responsible for review of medical history including menstrual history and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. Capable of giving signed informed consent as described in Section 10.1.4, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. *See country-specific requirement for France (FRA-1) in Section 10.8.*

5.2 Exclusion Criteria

Participants are excluded from randomization if any of the following criteria apply:

Medical Conditions

1. History of any major surgery within 8 weeks prior to screening or scheduled (elective) surgery, planned hospitalization and/or planned dental treatment during the study that could constitute a risk when participating in a study.
2. Severe invasive infections in medical history and/or active clinically significant viral, bacterial, fungal, or parasitic infection (systemic or severe skin infection) ≤ 3 months prior to the randomization visit.
   - Patients with a positive SARS-CoV-2-virus-RNA-test at Visit 2 (Day -8) or with any symptoms suspicious of COVID-19 or with contact to any SARS-CoV-2-positive patient/individual within 2 weeks prior to the SARS-CoV-2-virus-RNA-test at Visit 2 (Day -8).
     If a SARS-CoV-2 viral RNA test is indicated between Visit 2 (Day -8) and Visit 3 (randomization visit), start of study intervention should be delayed until test results exclude an infection.
   - Patients with a history of severe COVID-19 infection (i.e., requiring a hospital admission) independent of the time point.
   - Patients with a history of non-severe COVID-19 infection (i.e., not requiring hospital admission) ≤ 3 months prior to screening and/or without a full recovery (i.e., patients with clinically significant sequelae).
   - Symptomatic herpes zoster infection within 12 weeks prior to randomization visit or any history of disseminated/complicated herpes zoster (e.g., multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement, or postherpetic neuralgia).
3. A presence of uncontrolled condition including cardiovascular, respiratory, hepatic (see exclusion criterion 22), renal (see exclusion criterion 23), gastrointestinal, endocrine, hematological, neurological, or neuropsychiatric disorders or any other unstable illness that, in the opinion of the investigator, could constitute a risk when taking investigational product, study conduct or could interfere with the interpretation of data. Patients with stable asthma may be enrolled (stable asthma medication throughout study expected, see exclusion criterion 11).

4. Any clinically relevant abnormal findings in medical condition or history thereof or any deviation from normal laboratory values, physical examination, vital signs, 12-lead ECG at screening or randomization which in the opinion of the investigator, may put the participant at risk by participation in the study or provide difficulties in interpreting the trial data.
5. Participants with any of the following within 12 weeks of study entry: myocardial infarction, unstable ischemic heart disease or cerebrovascular accident.
6. Current or history of lymphoproliferative disease; or signs or symptoms suggestive of possible lymphoproliferative disease, including lymphadenopathy or splenomegaly; or active primary or recurrent malignant disease; or been in remission from clinically significant malignancy for < 5 years.

   The following exceptions to the above are acceptable for enrollment:

   a. Cervical carcinoma *in situ* that has been resected with no evidence of recurrence or metastatic disease for ≥ 3 years and
   b. Basal cell or squamous epithelial skin cancers that have been completely resected with no evidence of recurrence for ≥ 3 years.
7. Known immunodeficiency disorder or immunocompromised state or, in the opinion of the investigator, unacceptable risk for participating in the study.

Prior/Concomitant Therapy

8. Use of topical or systemic antihistamines within 7 days before Visit 3
9. Use of topical treatments for AD (i.e., topical glucocorticosteroids [TCSs] or topical calcineurin-inhibitors [TCIs] or topical JAK inhibitors) within 7 days before the randomization visit.
10. Start use of prescription emollients / moisturizers or emollients / moisturizers containing additives such as urea, ceramides, hyaluronic acid, heparinoid or any other active substances during the screening period or during the study.
11. Systemic immunosuppressive/ immunomodulating therapy (e.g., systemic glucocorticoids, cyclosporine, mycophenolate mofetil [MMF], methotrexate, azathioprine or oral Janus kinase (JAK)-inhibiting agents) or phototherapy within 4 weeks before the randomization visit. A stable daily dose of max. 1200 µg inhalative glucocorticosteroid (budesonide or equivalent) is allowed; this includes ‘reliever treatment’ expected to be required by the patient during the study.
12. Therapy with biologic drugs within 5 half-lives of the biologic drug (e.g. dupilumab or tralokinumab) or 12 weeks before randomization visit – whatever is longer –, except cell depletion therapy (within 6 months before the randomization visit). For vaccines, see “Other exclusions” below.
13. Use of drugs which might affect absorption of the study intervention (e.g., laxatives, loperamide, metoclopramide) during 1 week before the randomization visit.

14. Use of drugs within 1 week prior to the randomization visit which are substrates for Breast Cancer Resistance Protein (BCRP) (e.g., atorvastatin, daunorubicin, fluvastatin, gefitinib, hymecromone, imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, nitrofurantoin, pibrentasvir, pitavastatin, prazosin, rifampicin, rosuvastatin, simvastatin, sulfasalazine, sunitinib, topotecan, vincristine, zidovudine) (see also Appendix 10.6).
15. Use of drugs within 1 week prior to the randomization visit which are substrates for Organic Anion Transporting Polypeptide (OATP) 1B1 and 1B3 (e.g., ambrisentan, asunaprevir, atorvastatin, bosentan, cerivastatin, docetaxel, donoprevir, ezetimibe, fexofenadine, fluvastatin, gadoxetic acid, glibenclamide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, revefenacin, rosuvastatin, simeprevir, simvastatin) (see also Appendix 10.6).

Prior/Concurrent Clinical Study Experience

16. Current or previous (within 30 days of randomization visit) participation in a clinical trial involving an investigational product or non-approved use of a drug or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
17. Previous randomization in this study.

Diagnostic Assessments

18. Pregnancy (positive pregnancy test) or nursing at screening or randomization visit or considering becoming pregnant during the study.
19. Positive hepatitis B or C serology (unless curative treatment and HCV-RNA-negative). Subjects with positive HBsAb may be randomized provided they are hepatitis B-vaccinated and have negative HBsAg and HBcAb.
20. Positive HIV serology test.
21. Positive Quantiferon test for tuberculosis (i.e., QuantiFERON-TB Gold Plus test) at screening or participants with risk factors for TB and/or signs and symptoms suggestive for TB.
22. Chronic liver disease with evidence for liver fibrosis/cirrhosis (i.e., Class A, B and C based on Child-Pugh criterion) as documented in medical history or at least one of the following will be excluded:
    - Total bilirubin > 1.0 x ULN in the absence of Gilbert's Syndrome or hemolysis
    - ALT > 1.5 x ULN
    - AST > 1.5 x ULN.
23. eGFR < 60 mL/min/1.73 m^2 using the modification-of-diet-in-renal-disease (MDRD)* formula at screening.

    *calculated by the following MDRD equation:

    eGFR = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × 0.742 (if female) × 1.212 (if race is black).
24. Any of the following laboratory abnormalities at screening visit:

- Absolute neutrophil count below < 2.0 x 10^9 /L (< 200/ mm^3)
- Hemoglobin < 11 g/dL at screening.

Other Exclusion Criteria

25. Any planned or scheduled vaccination (excluding passive immunization) including COVID-19 vaccination during the study.
26. Receipt of live or attenuated vaccine 28 days prior to randomization visit.
27. Patients who received COVID-19 vaccine or influenza vaccine < 28 days prior to randomization visit.
28. History of chronic alcohol abuse, intravenous drug abuse, or other illicit drug abuse within the 2 years prior to the randomization visit.
29. Close affiliation with the investigational site, e.g. a close relative of the investigator, dependent person (e.g., employee of the investigational site).
30. Inability or unwillingness to make themselves available for the duration of the study and/or inability or unwillingness to follow study restrictions and procedures.
31. Known hypersensitivity to the study drug (active substance or excipients - croscarmellose sodium, mannitol, magnesium stearate, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, for details, see IB).

Re-screening

Re-screening of subjects is possible under certain circumstances. For details, see Section 5.4.

5.3 Lifestyle Considerations

It is recommended that intake of fluids should be relatively stable throughout study participation. As a precautionary measure, excessive exposure to sunlight such as sunbathing or the use of solarium should be avoided during the study period.

5.3.1 Meals and Dietary Restrictions

No specific food and drink restrictions apply.

5.3.2 Caffeine, Alcohol, and Tobacco

There are no specific lifestyle restrictions for caffeine, alcohol and tobacco.

5.3.3 Activity

It is recommended that participants should abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests.

5.3.4 Other Restrictions

Participants are asked to refrain from donating blood for the duration of their study participation. Also, participants should not engage in phototherapy or tanning in a booth/bed during the duration if the study.

5.4 Screen Failures

A screen failure occurs when a participant consents to participate in the clinical study but is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes informed consent date, date of last visit, demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new participant identification (PID).

Rescreening may occur for the following reasons (examples):

- The participant had successfully passed the screening procedures but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the participant's initial attempt to participate have been changed (via protocol amendment).
- The participant suffered from a temporary and not clinically relevant disease like a common cold.
- In the case of any of the following laboratory abnormalities (not within the screening period), screening tests may be repeated once within 2 weeks of the initial values, and values resulting from repeat testing may be accepted for eligibility:
  - Total bilirubin > 1.0 x ULN in the absence of Gilbert's Syndrome or hemolysis
  - ALT > 1.5 x ULN
  - AST > 1.5. x ULN
  - Absolute neutrophil count < 2 x 10^9 cells/L (< 2000/ mm^3)
  - eGFR < 60 mL/min/1.73m^2 (MDRD) formula
  - Hemoglobin < 11.0 g/dL
  - CK > 5 x ULN

In any case, the investigator has to ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. Also, for re-screening, the participant has to re-sign the informed consent form, even if it was not changed after the participant's previous screening.

5.5 Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

No specific criteria apply.

6 Study intervention(s) and Concomitant Therapy

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study participant during the study conduct.

6.1 Study Intervention(s) Administered

The study interventions administered for this trial are summarized in Table 6–1.

Table 6–1: Study interventions

Intervention Label	Zabedosertib	Placebo
Intervention Name	Zabedosertib; IRAK4 inhibitor	Placebo (matching to zabedosertib)
Intervention Description	120 mg tablet orally twice daily (BID) for 12 weeks	1 placebo tablet orally twice daily (BID) for 12 weeks
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	120 mg	not applicable
Dosage Level(s)	120 mg BID	BID dosing
Route of Administration	Oral	Oral
Use	Experimental drug	Control
Packaging and Labeling	Study intervention will be provided in HDPE bottles closed with child-resistant screw cap. Each bottle will be labeled as required per country requirement.	

HDPE = high-density polyethylene; IRAK4 = interleukin1 receptor-associated kinase 4

Tablets containing zabedosertib or corresponding placebo are identical in appearance (size, color, shape). In order to remain blinded, study interventions will be packaged in bottles labeled with a unique number which will be pre-printed on each bottle.

All participants will take study intervention (zabedosertib or matching placebo) BID (morning and evening doses) approximately the same time each day 12 hours apart.

Tablets are not to be broken, halved or crushed; they should be swallowed as a complete unit with water. Daily tablet intake should be done at home. At visits with PK, study drug intake of the morning dose should occur at the study site.

If a dose of study intervention has been missed:

- If up to 6 hours have passed since the dose was due, it should be taken immediately
- If more than 6 hours have passed since the dose was due, the dose should be skipped, and the next dose should be taken according to the regular schedule.

Table 6–2: Study Arms

Arm Title	Zabedosertib	Placebo
Arm Type	experimental	placebo
Arm Description	Participants will receive 120 mg zabedosertib BID for 12 weeks.	Participants will receive an equivalent number of tablets of matching placebo for 12 weeks.
Associated Intervention Labels	zabedosertib 120 mg	Placebo

6.2 Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm study interventions have been received and, if a temperature data logger has been included, appropriate temperature conditions have been maintained during transit. Any discrepancies are reported and resolved before use of the study intervention.

Only participants randomized in the study may receive study intervention and only authorized site staff may supply, prepare or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Drug returns, reconciliation and destruction information will be captured in the IRT.

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records. An adequate record of receipt, distribution, and return/destruction of all study treatment must be captured on the dispensing log and/or in the IRT.

Study drug tablets not returned will be considered to have been taken unless otherwise specified. At the end of the study, any remaining drugs will be collected and returned to the sponsor, destruction depot or destroyed at the site. Any discrepancies between the returned and expected returned study drugs should be explained.

Study intervention will be dispensed at the study visits summarized in SoA (see Section 1.3). Returned study intervention should not be re-dispensed to the participants.

6.3 Assignment to Study Intervention

Eligible participants who meet all the inclusion criteria and none of the exclusion criteria will be assigned a randomization number and randomly allocated in a 2:1 ratio to receive either zabedosertib or matching placebo.

The randomization will be done in blocks.

6.4 Blinding

As this is a double-blind study design, both investigators and participants will be blinded to study interventions.

All participants will be centrally assigned to randomized study intervention using Interactive Response Technology (IRT); the use of central randomization via IRT will minimize potential bias. Before the study is initiated, the directions for the IRT will be provided to each site.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the responsibility for determining if unblinding of a participant's intervention assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unblinding, the emergency unblinding requests are forwarded to the study specific emergency medical advice 24 hours / 7 days service. Participant safety must always be the first consideration in making such a determination. If

the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. In order to maintain the blind, study interventions will be packaged in bottles labeled with a unique number which will be pre-printed on each bottle.

Bioanalytical staff will be unblinded according to the corresponding Bayer standard operating procedure (SOP). Pharmacometrics and pharmacokinetics staff may also be unblinded according to Bayer SOPs. PK and exposure-response analysis might be performed using population approaches (popPK and popPK/PD, e.g. by non-linear mixed effect modeling). Analysis and report will be done under a separate cover if applicable. This evaluation might be started prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g. data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

6.5 Study Intervention Compliance

Participants will be requested to bring along all used and unused study intervention including packaging material to selected visit (see SoA, Section 1.3). Any discrepancies between actual and expected amount of returned study intervention or any discrepancies with the patient drug intake diary must be discussed with the participant at the time of the visit and should be resolved, if possible.

The data of participant's daily intake of study intervention will be collected as daily question on an electronic patient handheld device and reminders to take the study drug are planned to be sent via the device.

Further information about the participant's treatment compliance can be derived from drug concentration measurements.

6.6 Dose Modification

Dose modifications (dose and frequency of intake) of zabedosertib or placebo are not allowed during the intervention period of the study.

6.7 Continued Access to Study Intervention after the End of the Study

Participants who complete the treatment period or who are prematurely withdrawn from the study will not have further access to study intervention, and it will be up to the investigators discretion to provide follow-up medical care for all participants who complete the study or who are prematurely withdrawn from the study or refer them for appropriate ongoing care as required.

6.8 Treatment of Overdose

In this study, an overdose is defined as an intentional or accidental administration of zabedosertib, to or by a study participant, at a dose which is higher than the dose assigned to that individual participant according to the study protocol.

In the event of an overdose, no antidote or specific treatment is recommended. The investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Overdose per se will not be reported as an AE and/or SAE unless it is associated with clinically relevant signs and/or symptoms, or an intentional overdose taken with possible suicidal and/or self-harming intent (Section 10.3). In these cases, if feasible, a plasma sample for PK analysis may be obtained, ideally as soon as possible after the overdose, with recording of date and time of sampling.
- An overdose should be treated as clinically indicated based on signs and symptoms.
- Document the quantity of the excess dose as well as the duration of the overdose in the electronic case report form (eCRF/eDiary).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant has received within the last 30 days before randomization visit, is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

AD relevant medication (including emollients) will be recorded for 6 months before randomization visit.

Any SARS-CoV-2 vaccination prior to study entry should be recorded independent of the timeframe under prior/concomitant medication.

The sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

See Section 8, Screening, Medical history and AD history for information relating to previously used medications.

6.9.1 Background Therapy with Emollients / Moisturizers

All participants must use a stable amount (i.e., approximately the same amount for each application to the whole body at least twice daily) of emollient as background therapy during the course of the study, starting at least 7 days before the randomization visit. Any type of

emollient is permitted, but participants may not initiate treatment with prescription emollients / moisturizers or emollients / moisturizers containing additives such as urea, ceramides, hyaluronic acid, heparinoid, probiotics or any other active substances during the screening period or during the study. Participants may continue using stable amounts of such emollients / moisturizers, if initiated before the screening visit. Emollients used by the participant before entering the study should be continued with the same frequency/intensity. Participants will be reminded once a week about emollient usage by the electronic hand held device.

The emollient is considered an auxiliary medicinal product in this study (not an investigational product). The maximum daily amount and frequency of application should be agreed with the investigator and be in line with the user information.

The emollient will be locally supplied/reimbursed by the sponsor during the study, including follow-up, according to the locally agreed process.

Before the use of the defined topical rescue medication, investigators should attempt to manage participant's AD symptoms with emollients / moisturizers, e.g. with an increased frequency of use. If this is not successful or advisable, topical rescue treatment can be given to participants who are experiencing unacceptable or worsening symptoms of AD at any time after randomization visit.

For further information on the use of rescue medication, see also Section 6.9.2.

6.9.2 Rescue Medication

In the event of a disease flare or AD symptoms defined as any worsening of AD to an vIGA $\geqslant$ 3 requiring escalation of treatment confirmed by an investigator, which cannot be tolerated by the study participant, topical rescue medication as defined below may be used for a timeframe of several days at the discretion of the investigator. Before topical treatment for AD (= rescue medication) is initiated, the frequency of emollient use should be increased to try to control AD symptoms and efficacy assessments should be performed (see below and Section 8.1 [Unscheduled visit]).

Defined rescue medication for this study is the methylprednisolone aceponate (Advantan® cream). Only if Advantan cream is not available in the respective country, an alternative TCS with similar potency may be used (see WHO definition for potent corticosteroids group III, such as betamethasone, fluclorolone, desoximetasone, fluocinolone acetonide, budesonide, mometasone, beclomethasone, hydrocortisone aceponate). If TCSs are not tolerated or their use is not advisable, the topical TCIs pimecrolimus 1% (Elidel® cream) or tacrolimus (Protopic® 0.1% or 0.03% ointment) may be used.

The rescue medication is considered an auxiliary medicinal product (not an investigational product). The daily amount and frequency of application should be once daily for 1 week. If necessary, the duration of application may be extended to a maximum of 2 weeks. The use of rescue medication has to be documented in the CRF, providing information on product, dose, frequency and duration of therapy.

Topical rescue medication will be locally supplied/reimbursed by the sponsor during the study, including follow-up, according to the locally agreed process. Whenever possible, the efficacy assessments using the EASI, vIGA-AD and BSA affected by AD should be performed immediately before start of topical rescue therapy and at its end. Site visits

(scheduled or unscheduled) are therefore strongly recommended before start of rescue treatment.

If topical rescue medication is used, study intervention (zabedosertib or placebo) will be continued and study visits performed according to the SoA (see Section 1.3).

6.9.3 Prohibited Medication and Therapies

Prior and concomitant therapies not permitted in this study are listed in Section 5.2, exclusion criteria. Therapies listed in the exclusion criteria are also prohibited during the study (exception: TCSs and TCIs may only be used as rescue medication).

In addition, the use of antihistamines and live vaccination are not allowed during the study.

If the participant took a prohibited medication or used a prohibited non-drug therapy for any reason, the investigator should consult with the sponsor to determine if the participant should be withdrawn from study intervention and/or the study.

For the purpose of efficacy analysis, participants receiving any pharmacologically active non-study medication or phototherapy for AD will be considered as treatment failures after the start of such medication, except for the use of defined topical rescue medication up to/including Week 8. Whenever possible, efficacy and safety assessments according to Visit 7 (EOT) should be conducted immediately before administering any systemic medications for AD or initiation of phototherapy (= SoC). For zabedosertib, a wash-out period of 7 days (approximately 5 half-lives) is recommended, because there is no experience or data with a combination of zabedosertib and systemic AD treatment.

SoC should be reserved for participants who do not respond adequately to topical treatment (at least 7 days of use). If a participant receives SoC treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, MMF, azathioprine, baricitinib etc.) dupilumab, tralokinumab or initiation of phototherapy, study intervention has to be discontinued and EOT assessments including FU visits performed.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for EOT and FU assessments, as described at the end of this section. See the SoA (see Section 1.3) for data to be collected at the time of discontinuation of study intervention and FU and for any further evaluations that need to be completed.

If an exclusion criterion is met during the study, the investigator should consider discontinuation of the participant's study intervention, if medically indicated.

The participant's study intervention must be permanently discontinued, if anything of the following occurs:

- Pregnancy (see also Section 8.4.5).
- Participant receives SoC treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs or phototherapy (see also Section 6.9.3).
- Participant interrupts study intervention for more than 10 consecutive days (see also Section 7.1.4).
- Participant experiences an AE which is considered to be related to study treatment or study procedure and, in the investigator's judgment, is severe enough in nature to warrant treatment discontinuation. Common Terminology Criteria for AEs (CTCAE) current version, Grade 3 or higher (may be used as guidance).
- Any malignancy.
- Febrile illness for more than 48 hours and clinical or biochemical signs of infection (e.g., clinically relevant abnormality of hsCRP level).
- Participants who received COVID-19 vaccine during the study treatment phase, must be withdrawn from the study. An interval of at least 14 days between the last study drug and the vaccine dose is recommended.
- Positive SARS-CoV-2 viral RNA test or clinical evidence for COVID-19 during the study despite a negative test result (study intervention should be interrupted until test results are available). Testing during the study should be done on an individual basis as medically indicated according to local practice, triggered by signs and symptoms of a potential SARS-CoV-2 infection or contact history. If current COVID-19 infection is confirmed, the participant must be permanently discontinued from study intervention.
- The participant's randomized treatment assignment is unblinded by the investigator or treating physician.
- Sponsor request (after discussion with the investigator), for reasons such as a significant protocol deviation or participant non-compliance.
- Study as whole is terminated by the sponsor.
- Liver safety-related discontinuation criteria are met as described in Section 7.1.1.
- Confirmed creatine kinase (CK) > 10 x ULN or clinical signs of rhabdomyolysis (Section 10.2.1).
- Herpes zoster

A participant should also be permanently discontinued from study intervention for the following **laboratory abnormalities**:

- WBC count < 1000 cells/µL; < 1.0 x 10^9 /L
- Absolute neutrophil count < 500 cells/µL; < 0.5 x 10^9 /L
- Lymphocyte count < 200 cells/µL; < 0.2 x 10^9 /L
- Hemoglobin < 8 g/dL.

Handling of discontinuation of study intervention

For participants who permanently discontinue the study intervention, an EOT visit with all assessments as specified in the SoA (see Section 1.3) should be performed as soon as the study intervention has been discontinued. If the decision to stop the study intervention early is

taken during a site visit, this visit becomes the EOT visit. The FU visit should be performed as planned after the last dose.

After the early EOT visit, treatment with SoC may be started at the discretion of the investigator and entered into the eCRF. For zabedosertib, a wash-out period of 7 days (approximately 5 half-lives) is recommended, because there is no experience or data with a combination of zabedosertib and systemic AD treatment.

See the SoA (Section 1.3) for data to be collected at the EOT and FU and for any further evaluations that need to be completed.

7.1.1 Liver Chemistry Stopping Criteria

Permanent discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined below or in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant:

- ALT or AST > 3 x ULN **and** total bilirubin (TBL) > 2 x ULN
- ALT or AST > 3 x ULN **and** INR > 1.5 x ULN [a]
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 8 x ULN

[a] Relevant only if the participant is not on Vitamin K antagonist, new oral anticoagulants (NOACs) or heparin.

- Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.2 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. A review of the ECG at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3 Temporary Discontinuation

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of AEs or abnormal laboratory values that may have an unclear relationship to investigational study drug.

Reasons for temporary discontinuation may include the following:

- Skin infection such as impetigo

- Participant experiences an AE that does not resolve promptly with supportive care and which is consistent with specific Common Terminology Criteria for AEs (CTCAE) current version, Grade 2 (may be used as guidance)
- If a SARS-CoV-2 viral RNA test is indicated during this study, it should be done according to local standards and regulations. If initiated by the investigator the study central lab or local lab may be used for the SARS-CoV-2 viral RNA test. The study intervention should be discontinued until test results exclude an infection. The participant may resume study intervention at the discretion of the investigator.
- Abnormal laboratory findings: (to monitor closely and if the abnormal results persist after a second assessment, participant must be temporarily discontinued from the study drug. (For permanent discontinuation criteria, see Section 7.1.)
  - WBC count < 2000 cells/µL; < 2.0 x 10^9/L
  - Absolute neutrophil count < 1000 cells/µL; < 1.0 x 10^9/L
  - Lymphocyte count < 500 cells/µL; < 0.5 x 10^9/L
  - Hemoglobin < 10.0 g/dL
  - ALT or AST > 3 x ULN after start of study intervention
  - ALT or AST value 2-fold increases above the lowest baseline value for participants with elevated liver enzymes before drug exposure.

7.1.4 Temporary Discontinuation and Restart of Study Medication

Regarding potential resuming of interrupted study intervention, the following rules apply:

- Discontinuation of up to 10 consecutive days:
  → Resume study intervention intake as planned
- Discontinuation for more than 10 consecutive days:
  → Participant must permanently discontinue study intervention.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request, for any reason (or without providing any reason)
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, the EOT and FU visits should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation (EOT) and FU and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.1).

8 Study Assessments and Procedures

8.1 Administrative and General Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Patient-reported outcomes as listed in Section 8.2.2 will be provided in local language, and in the case of completion at the study site they should always be completed by the study participants prior to any activities at site.

- In the event of a significant trial-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority / ethics requirements.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is not expected to exceed 180 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Unscheduled visit(s)

Participants who experience a suspected AD flare/relapse between scheduled study visits will return to the clinic for an unscheduled visit to determine if AD flare/relapse is confirmed

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any AD treatment prohibited in the study (see Section 6.9.3) or rescue medication (see Section 6.9.2). An unscheduled visit may be used for this purpose, if necessary.

Screening (population characteristics)

Demography

Subject to local legislation, the following information will be collected for demography in the eCRF: Year of birth, age, sex, ethnicity and race.

Medical history and AD history

All relevant information on medical history including history of COVID infection(s), history of AD and associated comorbidities will be collected in the eCRF at screening.

History of AD will include: Date of AD diagnosis, number of AD flares and episodes of skin infections requiring pharmacological treatment within the last year prior to screening, history of asthma, allergic rhinitis and allergic conjunctivitis.

Any SARS-CoV-2 vaccination prior to study entry should be recorded independent of the timeframe under prior/concomitant medication.

8.2 Efficacy Assessments

Efficacy will be assessed using clinical outcome assessments (COAs) including ClinROs and PROs, as well as objective methods. Planned time points for all efficacy assessments are provided in the SoA.

A ClinRO is a measurement based on a report that comes from a trained health care professional after observation of a patient's health condition. In this trial, ClinROs will be used for the assessment of primary, secondary and exploratory efficacy endpoints. It is recommended to have skin-related assessments performed by the same trained dermatologist or under his/her supervision. All investigators will be trained prior to the start of the study (see Section 8.2.1).

ClinRO assessments include:

- EASI
- vIGA-AD
- BSA affected by AD.

A patient-reported outcome (PRO) is a measurement based on a report that comes directly from the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else. In this trial, language/country versions of the PROs will be used for the assessment of secondary and exploratory endpoints collected using an electronic patient handheld device during the entire study duration (including days of the study visits) without interaction with the investigator.

The PRO instrument used for assessments of efficacy is:

- Peak Pruritus 0-10 NRS.

An overview on the different measurements and the planned time points for all efficacy assessments is provided in the SoA (Section 1.3).

8.2.1 Clinician-Reported Outcomes (ClinROs)

Before the start of the study at the individual site, all investigators are or will be trained for the use of all clinician reported outcomes (ClinROs). During the study and in accordance with the SoA, the investigator will enter the results into an electronic device provided to the study site.

All ClinROs can be considered "fit for purpose". The responder definitions used for the efficacy endpoints in this study are robust.

8.2.1.1 Eczema Area and Severity Index (EASI)

The EASI is a ClinRO assessing the extent of AD at four body regions (head and neck, trunk and upper and lower extremities) by measuring the average severity of four clinical signs at each body region: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale of 0 to 3 (Hanifin et al, 2001).

For scoring, the sum of these severity scores for each region is multiplied by a region score, a value of between 0 and 6 representing the percentage of skin affected by eczema, and finally weighted by a body region dependent multiplier (0.1 for head/neck; 0.3 for trunk, 0.2 for upper extremities and 0.4 for lower extremities). This provides an EASI score per body region, with the final EASI score being the sum of the 4 region scores. The minimum EASI score is 0 and the maximum EASI score is 72, with a higher score indicating worse severity of AD. A scoring table can be found in Figure 10–1.

The EASI 75 will be assessed as the primary efficacy endpoint.

8.2.1.2 Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD)

The vIGA-AD is a 1-item static ClinRO using a 5-point scale from 0 (clear) to 4 (severe) based on 4 clinical features of AD lesions: erythema, induration/papulation, lichenification, and oozing/crusting, and takes extent of disease into account (Simpson et al, 2020). A scoring table can be found in Figure 10–2.

In this study, the vIGA-AD will be a secondary endpoint.

8.2.1.3 Assessment of Body Surface Area (BSA) Affected by Atopic Dermatitis

BSA affected by AD will be assessed for each section of the body, e.g. using the rule of nines. The possible highest score for each region is:

Head and neck:	9%
Anterior trunk:	18%
Back:	18%
Upper limbs:	18%
Lower limbs:	36%
Genitals:	1%.

Affected BSA will be reported as a percentage of all major body sections combined.

Overall, the BSA has shown appropriate measurement properties and is widely used in clinical practice and research. The BSA may provide important information about the AD severity and is considered appropriate for use to assess secondary efficacy endpoints in this study.

8.2.2 Patient-Reported Outcomes (PROs) – General Information

In this clinical trial, efficacy on the most important symptom, itch will be assessed by the study participants themselves and is therefore considered a PRO.

The Peak Pruritus 0-10 NRS will be collected daily in the morning if possible (collection is possible later in the day as well) on the electronic handheld device (ePRO) at home.

The Peak Pruritus 0-10 NRS was developed by Yosipovitch et al, 2019 and is a single patient-reported item designed to measure peak pruritus (itch), or 'worst' itch, over the previous 24 h based on the following question: 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?'(see Figure 10–3.)

≥ 4 points reduction of the Peak Pruritus 0-10 NRS is considered a clinically relevant within-person response.

In this study, the Peak Pruritus 0-10 NRS will be assessed electronically every day during the entire study period in accordance with the SoA.

This tool can be considered "fit for purpose". The responder definitions used for the efficacy endpoints in this study are robust.

Time for completion

Time for completion of each item of the PRO is conservatively estimated with approximately 30 seconds per individual item. The daily completion time at home, therefore, is approximately 30 seconds.

Dispense of the patient handheld device, data entry and transmission

During screening Visit 2, study participants will be provided with a training on the use of the patient handheld device. The participants will be asked to confirm their understanding on the use of the device and completion of the ePRO before the handheld device is activated and dispensed to the study participants at the screening Visit 2.

The specific time window for data entry into the patient handheld device is ePRO-specifically technically regulated and alarms will be set as appropriate to remind the study participant to complete the ePRO respectively.

Participants' data entries from the patient handheld device will be transmitted by wireless connection to the electronic diary provider's database and on systematic basis to Bayer AG. Automatic continuous checking of the data transfer will be performed, and completeness of diary entries will be monitored, so that a failure to make entries is detected by the data-logging system and a warning will be sent to the study site. The ePRO device will be returned to the site as soon as a participant leaves the study.

Training of study participants

Study participants will be educated during all study visits regarding the importance of their in-time correct completion of the ePRO especially the daily completion. Standardized technical training for the use of the patient handheld device at screening Visit 2 and randomization visit and ongoing technical support during the entire study duration will be provided by the study site staff to prevent missing data entry to the extent possible. Beyond this technical support, no other help should be given to study participants regarding the completion of the 0-10 peak pruritus NRS and the study participant will be instructed to complete the ePRO on their own.

Training of and by study site staff, 24-hour help desk

The study site staff will be instructed to explain to the study participants the importance of completing the ePRO on the patient handheld device.

The study site staff will be trained regarding the use of the patient handheld device, and in resolving technical issues with the patient handheld device during the Investigator Meeting and site initiation process. Educational material will be available in the Investigator Site File. The study site staff will provide a standardized technical training on the handling of the patient handheld device to the study participants during screening visit 2 and will assist the study participants in case of any technical queries during the entire study duration.

In addition to the technical support by the study site staff, a 24-hour help desk by the ePRO provider will be available during the entire study duration to respond urgent technical questions.

Measures to further prevent missing patient handheld device entries

When the study site becomes aware of missing patient handheld device entries, the study site staff will contact the study participant who has missed 2 consecutive daily entries as soon as possible and ask for reasons for failure in data entry and transfer. The study site staff will remind the study participants the importance of daily diary entry.

Further to the automatic continuous checking of completeness of the patient handheld device entries, at all the study visits following screening Visit 2, the patient handheld device entries will be checked by the study site personnel for completeness.

<u>Assessment of efficacy</u>

In this study participants achieving a 4-point improvement in the Peak Pruritus 0-10 NRS for participants with Peak Pruritus 0-10 NRS ≥ 4 at baseline will be assessing a secondary efficacy endpoint.

Further secondary and other pre-specified endpoints will be assessed using the Peak Pruritus 0-10 NRS.

<u>Eligibility</u>

For decision on participants' eligibility, the average of the Peak Pruritus assessed during the 7 days immediately preceding randomization will be calculated. A minimum of 4 daily scores out of the 7 days is required to calculate this baseline score for the peak pruritus. For participants who do not have at least 4 daily scores reported during the 7 days immediately

preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

Physical examinations will be conducted according to the schedule provided in the SoA.

- A **complete** physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems.
- A **symptom-directed** physical examination will be performed according to the signs and/or symptoms reported by the participant; therefore, it may vary with each visit.

Height will be documented at screening. Weight will be measured at the time points given in the SoA.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

Vital signs will be assessed according to the schedule provided in the SoA (see Section 1.3).

Vital signs will be measured in a sitting position after 10 minutes rest and will include body temperature, systolic and diastolic blood pressure, and pulse rate.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) or as clinically indicated using an ECG machine that automatically measures the ECG mean ventricular rate, PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTcB withdrawal criteria and any additional QTcB readings that may be necessary.

ECG for each participant should be obtained using the same electrocardiograph machine whenever possible. To minimize variability, participants should remain in a resting position for at least 5-10 minutes prior to each ECG recording.

Quality of ECGs should be assessed immediately and in case of improper quality of an ECG another ECG(s) should be recorded to replace the improper ECGs, which would be documented as invalid by the investigator.

For each ECG, the investigator has to perform a thorough review that may result in ECG findings and an overall assessment (including clinical relevance) deviating from the automated device output.

Each ECG will be evaluated for the overall normality as follows:

- Normal
- Abnormal, clinically insignificant
- Abnormal, clinically significant.

Only the results of this local review will be entered as findings into the electronic CRF and any clinically relevant abnormality should be documented as an AE or SAE. ECG findings observed before first study intervention intake that reflects any previous cardiovascular

disease (e.g., atrial fibrillation, previous myocardial infarction or any abnormality in the electrical conduction system) should be documented as medical history.

ECG recordings will be kept as part of subjects file at the site as per site practice.

8.3.4 Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

  Note: If screening laboratory assessments were done at Visit 1, only CRP, blood count, and urinalysis must be re-assessed at Visit 2.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.
- Laboratory abnormalities leading to discontinuation of study intervention are listed in Section 7.

8.3.5 Pregnancy Testing

The defined time points for pregnancy testing are displayed in the SoA (see Section 1.3).

Zabedosertib was non-genotoxic. In addition, it did not show a phototoxic potential.

In the developmental toxicity studies in mice, effects on fetuses were seen starting at the low dose with a higher incidence of cleft palates at the high dose. No effects were seen in the pilot and pivotal embryofetal development studies in rabbits up to the maximum feasible dose tested.

A central laboratory (serum test) will be used for the pregnancy testing during screening (Visits 1 and 2) and at EOS for all WOCBP (Section 10.4). Further pregnancy tests (urine test) will be performed locally for all WOCBP at the time points in the SoA.

8.3.6 Suicidal Ideation and Behavior Risk Monitoring

Severe AD is associated with increased suicidality and suicidal ideations (Sandhu et al, 2019). Therefore, assessment of suicidal ideation and behavior will be monitored during the study by the investigators as part of the clinical routine in managing adult patients with moderate-to-severe AD.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

The definition of unsolicited and solicited AEs can be found in Section 10.3.1.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7). This includes events reported by the participant.

AEs are considered to be treatment-emergent if they have started or worsened after first administration of study intervention until 7 days after the last intake of the study intervention.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

(S)AEs will be collected from the start of study intervention until the last FU visit (28 days after EOT) at the time points specified in the SoA (Section 1.3). (S)AEs which are related to protocol-required study procedures (e.g., (S)AE related to invasive study procedures) will be recorded as (S)AEs from the signing of the ICF.

Any medical occurrences/conditions that begin in the period between signing ICF and the start of study intervention, and which are not related to a protocol-required study procedure, will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in Section 8.4.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB) / Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and in female partners of male participants will be collected after the start of study intervention and until last safety FU visit, but at least until 2 weeks after the last dose of study intervention in case of early termination.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant / pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in

Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, the investigator may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.4.6 Cardiovascular and Death Events

BAY 1834845 and its metabolite M-5 (BAY 2822815) did not show activity at potential off-targets and did not interact with cardiac ion channels (human ether-à-go-go-related gene [hERG], human sodium channel/current isoform 1.5 [hNav1.5], and human calcium channel/current isoform 1.2 [hCav1.2]).

In-vivo, BAY 1834845 was devoid of acute adverse effects on vital organ functions in rats (central nervous and respiratory system), and in both Beagle dogs and Cynomolgus monkeys (hemodynamic and electrocardiogram parameters).

In the FiM study (18384), no TEAEs were reported relating to changes in vital sign values nor to cardiac-related symptoms following treatment with zabedosertib.

In the drug interaction study (18387, Part B), one subject had documented palpitations; there were no subjects with clinically significant ECG findings, and no further TEAEs were reported relating to changes in ECG values following treatment with zabedosertib.

In the multiple dose study (18385), one subject had documented palpitations; there were no subjects with clinically significant ECG findings, and no further TEAEs were reported relating to changes in ECG values following treatment with zabedosertib. No new safety findings related to cardiovascular and death events were identified from Study 21329.

8.4.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8 Adverse Events of Special Interest

Adverse events of special interest (AESIs) will include:

- Confirmed or suspected severe invasive bacterial infections
- Systemic hypersensitivity reactions
- Non-invasive infections (skin)
- Unexplained cases of rhabdomyolysis

AESIs must be reported in an expedited fashion as described for SAEs in Section 10.3.4.

8.5 Pharmacokinetics

8.5.1 PK measurements of zabedosertib and its metabolite M-5

Sparse blood samples for PK analyses of zabedosertib and its metabolite BAY 2822815 (M-5) in plasma will be collected at the time points given in the study SoA (Section 1.3). Details about the collection, processing, storage and shipment of samples for PK analyses will be provided separately (e.g., sample handling sheets or laboratory manual) and available at the Investigator Site File.

The PK analyses will be performed using validated analytical methods. Quality Control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration samples and QC samples will be reported in the Bioanalytical Report, which will be included in the Clinical Study Report for this study. Concentrations are calculated from the chromatographic raw data in accordance with current Bayer guidelines.

The PK evaluation, if applicable, will be based on the actual sampling and dosing times.

Blood samples will be considered valid for the population PK analysis (see below) under the following conditions:

1. The dose amount and time of drug intake prior to the blood sample is known
2. The time of the blood sample collection is known

Therefore, it is important to have these data thoroughly documented in the CRF. Deviations from the specified time points are possible and should not be considered as protocol violations. Exact collection dates and times of the PK samples and the times of the evening and morning doses of the previous day as well as the time of the morning dose on the visit day must be documented. In addition, to reassure PK results drug measurements may be performed from samples taken for other laboratory investigations (e.g., safety lab). The results of those measurements will be reported internally in the PK study file.

No non-compartmental analysis assessment will be performed. Measured concentrations will be listed and presented by descriptive statistics.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel. The bioanalyst will remain unblinded for analysis of study samples.

8.5.2 Population pharmacokinetic (popPK) evaluation

The variability in the pharmacokinetics of zabedosertib (and optionally its metabolite BAY 2822815), drug-related pharmacodynamic (PD) biomarker and/or safety and efficacy measurements collected during the trial might be analyzed using nonlinear mixed effects modeling.

Mixed effects models, e.g. population pharmacokinetic (popPK) models, describe the relationship between dose and time and variables such as drug plasma concentrations or clinical response. Both structural and random effects are involved in this relationship. A previously developed population PK model based on phase-1 data will be further developed to evaluate the variability in PK based on intrinsic factors (e.g., body weight, race) and extrinsic factors (e.g., concomitant medication) (covariates) that are of clinical relevance. If applicable, a separate Modeling and Simulation (M&S) analysis plan, providing details of the

model development and evaluation will be provided prior to the beginning of the population PK analysis and results will be presented in a separate M&S Report.

The population PK analysis might start prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g. data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

PK/PD and/or exposure-response evaluations might be conducted to evaluate the relationship between zabedosertib pharmacokinetics and or exposure and specific PD and/or safety and/or efficacy measures. If applicable, a separate M&S analysis plan, providing details of the methodology and evaluation will be provided prior to the beginning of the PK/PD and/or exposure-response analysis/ analyses and the results will be presented in a separate M&S Report(s).

The PK/PD and/or exposure-response evaluations might start prior to database lock. If this is applicable, appropriate measures will be taken to maintain blinding of the study team, e.g. data will be stored separately, and members of the study team will neither have access to the randomization list nor to individual data.

8.6 Pharmacodynamics

None.

8.7 Genetics

In this study, no genetic sampling will be performed.

8.8 Biomarkers

In this study, genetic as well as non-genetic biomarkers will be investigated.

Table 8–1: Sample types for biomarkers

Skin biopsy substudy (formalin fixation)	Skin sample 1	IHC (protein expression)
Skin biopsy substudy (RNA fixation)	Skin sample 2	mRNA expression
BM plasma	Blood sample 1	Inflammatory markers / other exploratory BMs
BM whole blood	Blood sample 2	e.g. Kinase activity

BM = biomarker; (m)RNA = (messenger) ribonucleic acid; IHC = immunohistochemistry

- Timing – see SoA (Section 1.3) for planned time points of sample collection.
- Sample handling and storage – details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g., lab manual). Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the sponsor to enable further analyses.
- Medical history information – if any additional information about the status of disease was collected in the course of treatment prior to entry of the participant in the study, the results may be collected in order to include this data in biomarker analyses.

- Reporting – the results of biomarker investigations may be reported separately (e.g, gene expression analysis of skin biopsies in a biomarker evaluation report).

An exploratory biomarker (BM) analysis will be conducted in this study. The sample types are summarized in Table 8–1.

Skin biopsy samples will be collected from a subgroup of participants willing to participate in this substudy, independent of the study intervention (n = approximately 40) at time points defined in the SoA. See Section 10.5.

8.8.1 Biomarkers Monitoring Disease Activity

AD is the most common, complex chronic inflammatory skin disease. PD biomarkers will be evaluated in samples collected before and during treatment in order to determine the impact of the study intervention on these biomarkers.

Candidate PD biomarkers may give hints to drug efficacy and may include (but are not limited to) for example:

- Skin biopsies: Molecular analysis (gene expression (customized host response panel [NanoString] with addtl. AD-specific probes); immunohistochemistry (eg K16, Ki 67), optional analysis) of the lesional skin biopsies will be performed. in a substudy (n = approximately 40 planned). See Section 10.5.
- Blood: Plasma levels of inflammatory markers and kinase activity (optional analysis).

In addition, a blood sample may be subjected to a further inflammatory BM analysis in order to identify biomarkers which respond to treatment or biomarkers which may indicate disease progression (optional analysis).

8.8.2 Other Biomarkers

BMs related to the mode of action or the safety of zabedosertib may be examined in addition to the BMs described above.

Further BMs deemed relevant to atopic dermatitis or other inflammatory diseases of the skin and associated health problems may be examined in addition to the BMs described above. Those investigations may include, e.g. diagnostic, safety, PD, monitoring, or potentially predictive BMs.

8.9 Immunogenicity Assessments

See Section 8.4.8.

8.10 Health Economics

Health economics parameters are not evaluated in this study.

8.11 Other Procedures

Photographs of a representative area of AD involvement (e.g., the lesioned area used for EASI assessments) may be taken on an individual basis at selected sites (optional procedure) to exemplary document the course of disease during the study. The photographs taken in this study are primarily planned to be used for publication purposes. The sponsor will check the quality of the received image data. Instructions for taking the photographs (for timepoints, see SoA in Section 1.3) will be provided and available in a specific manual.

9 Statistical Considerations

The analysis and reporting will be done on all data from all participants at the time the study ends.

The statistical analysis plan will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypothesis

The primary efficacy endpoint is achievement of 75% reduction from baseline in the EASI (EASI 75 response) at Week 12 (Day 84, EOT).

Let π_{BAY} and π_{Plac} be the responder rate with respect to EASI 75 after zabedosertib and placebo, respectively.

The statistical hypothesis of the study is defined as follows:

$\pi_{BAY} > \pi_{Plac}$ ('clinical activity' criterion),

i.e. that the EASI 75 responder rate after treatment with zabedosertib is higher than after placebo.

The study will be evaluated using Bayesian statistics, which allows to determine the posterior probability in favor of a hypothesis. Therefore it is not needed to specify a pair of hypotheses. The statistical hypothesis will be considered accepted if the posterior probability for the hypothesis of interest is higher than 90%.

9.2 Analysis Sets

The analysis sets are defined in Table 9–1.

Table 9–1: Analysis sets

Analysis set	Description
Enrolled	All participants who signed the ICF.
All Randomized (RAND)	All participants randomly assigned to study intervention Participants will be analyzed according to the intervention they were randomized to.
Safety analysis set (SAF)	All participants who took at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Per protocol set (PPS)	All randomized participants who meet the following criteria: – have an EASI score at baseline – have an EASI score at Day 56 (Visit 6) or later or took rescue medication between Day 56 (Visit 6) and Day 84 (Visit 7) or took SoC or discontinued study intervention due to lack of efficacy (at any time) – showed compliance of at least 80% with study intervention between start of treatment and end of treatment or start of rescue medication at or after Day 56 (Visit 6), whatever comes first – showed compliance of at least 80% with study intervention during the last 4 weeks before end of treatment or start of rescue medication at or after Day 56 (Visit 6), whatever comes first. – are without validity findings with respect to the efficacy related entry criteria Participants will be analyzed according to the treatment they actually received.
Pharmacokinetic set (PKS)	All participants who – were treated with zabedosertib, – have at least 1 valid zabedosertib plasma concentration sample, – are without protocol deviations, which would interfere with the evaluation of the PK data. See Section 8.5.1 for PK details

Details on additional analysis sets which may be of interest will be provided in the SAP.

The assignment of participants to the analysis sets will be decided before unblinding.

9.3 Statistical Analyses

The SAP will be finalized prior to unblinding (the final SAP is prerequisite for Blind Review Meeting), and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and specific secondary endpoints. If not otherwise indicated, the statistical analyses will be performed using the Statistical Analysis System (SAS); the version used will be specified in the SAP.

9.3.1 General Considerations

Continuous variables assumed to be normally distributed will be summarized using number of participants, mean, standard deviation, minimum, median, and maximum. Continuous variables assumed to be log-normally distributed will be summarized using number of participants, geometric mean, geometric standard deviation, geometric coefficient of variation, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, minimum, median, and maximum.

For categorical data frequency tables will be provided.

In general, summary statistics and frequency tables will be presented by treatment group, visit and time point (if applicable). Plots over time (if applicable) will also be presented by treatment group.

9.3.2 Efficacy Analyses

The primary efficacy analysis will be performed on the PPS.

9.3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is achievement of 75% reduction from baseline in the Eczema Area and Severity Index (EASI 75 response) at Week 12 (Day 84). The EASI score ranges from 0 to 72. The lower the EASI score the better the state of the participant with respect to severity and extent of AD symptoms.

The analysis of the primary efficacy endpoint on the PPS will be performed as follows:

The impact of a potential use of rescue medication (TCSs or TCIs) or SoC for treatment of AD on the efficacy effect will be accounted for as follows:

If rescue medication is used between Day 56 (Visit 6) and Day 84 (Visit 7) or if SoC is used (at any time), the participant will be specified as a non-responder with respect to the EASI 75 response from the time the rescue medication or SoC medication is used.

If a participant discontinues study intervention due to lack of efficacy at any time (e.g., due to an adverse event related to AD such as disease flare), the participant will also be specified as a non-responder with respect to EASI 75 response from the time of the discontinuation.

Otherwise, missing data - e.g. due to study intervention discontinuation due to other reasons such as reasons related to Covid-19 pandemic (individual reasons or prevention/logistic measures), withdrawal of consent not due to lack of efficacy or adverse events not related to AD - will be imputed using a multiple imputation approach based on logistic regression model. Details will be specified in the SAP. Furthermore, alternative imputation methods might also be specified in SAP.

The following supplementary analyses will be performed to further assess rescue medication use. The study participant is considered a non-responder in case of rescue medication use between the EOT visit and

- baseline
- 1 week after baseline,
- 2 weeks after baseline,
- 4 weeks after baseline,
- 6 weeks after baseline.

One additional analysis will be performed where rescue medication does not trigger the classification as non-responder at all to assess the effect of combined treatment of zabedosertib with topical AD medication.

Participants who take SoC medication or who discontinue study intervention due to lack of efficacy will still be counted as a non-responder for the time points after SoC use or discontinuation of study intervention due to lack of efficacy as described above.

Bayesian inference will be used to quantify the EASI 75 responder rates on Day 84 in the zabedosertib and placebo treatment group. For each treatment group a non-informative Beta(1,1) prior will be used. The Beta(1,1) prior produces a posterior distribution in the same distribution family, namely Beta(k+1,n-k+1) with k being the number of EASI 75 responders in the respective treatment group and n being the number of all participants in the respective treatment group. Simulations based on the posterior distributions of the EASI 75 response rate in both treatment groups will then be used to calculate the posterior probability $P(\pi_{BAY} > \pi_{Plac} | \text{data})$. In addition, median and 90% and 95% credible intervals will be calculated based on the posterior distributions for the response rates in both treatment groups as well as for the difference between both treatment groups.

9.3.2.2 Secondary Efficacy Endpoints

For binary endpoints, the secondary efficacy analysis will use the same approach as for the primary analysis.

In detail, the proportion of participants reaching EASI 50 response at Week 12 (Day 84) will be analyzed. An EASI 50 response is defined as achievement of 50% reduction from baseline in the Eczema Area and Severity Index.

Likewise, the proportion of participants reaching EASI 90 response at Week 12 (Day 84) will be analyzed. An EASI 90 response is defined as achievement of 90% reduction from baseline in the Eczema Area and Severity Index.

Furthermore, the proportion of participants with a response with respect to vIGA-AD at Week 12 (Day 84) will be analyzed. A vIGA-AD response refers to achievement of a vIGA-AD of 0 or 1 with at least a 2-grade reduction from baseline (vIGA-AD scale ranges from 0-4).

In addition, the proportion of participants with a response with respect to the average of the Peak Pruritus 0-10 NRS at Week 12 (Day 84) will be analyzed. A response with respect to peak pruritus will be defined as achievement of a ≥4 point improvement (reduction) in the weekly average of the Peak Pruritus 0-10 NRS score from baseline (for participants with Peak Pruritus 0-10 NRS score ≥ 4 at baseline) (Phan et al, 2012).

For continuous endpoints, i.e. percent change from baseline in EASI score, absolute change from baseline in BSA as well as percent change from baseline in the weekly average of the Peak Pruritus 0-10 NRS score , the impact of a potential use of rescue treatment or SoC for treatment of AD on the efficacy will be accounted for as follows:

If rescue medication is used between Day 56 (Visit 6) and Day 84 (Visit 7) or if SoC is used (at any time) or study drug is discontinued due to lack of efficacy (at any time), data collected afterwards will be handled as missing.

Missing data will be imputed using a multiple imputation approach followed by an analysis of covariance model. Further approaches for imputation might be defined in the SAP.

A mixed-effect repeated measurement model will be applied. This model will include the respective continuous efficacy endpoint as dependent variable. All post-dose data will be included in the model. The model will include the respective baseline value as covariate, treatment group, visit and the interaction of visit and treatment group (visit*treatment group) as fixed effects. The covariance structure will be assumed to be unstructured, but the same for both treatment groups. The structure of the covariance matrix might be adapted, e.g. in case of convergence problems. The treatment difference (including 95% confidence intervals) at the

planned end of treatment at Day 84 (Visit 7), as well as at the other time points, will be calculated by appropriate contrasts from the mixed-effect repeated measurement model.

9.3.3 Safety Analyses

All safety analyses will be performed on the SAF.

9.3.3.1 Secondary Endpoint - Safety

The secondary safety endpoint is the frequency and severity of TEAEs.

TEAEs are events that start after the first treatment with the study intervention and until 7 days after the last intake of study intervention. All TEAEs will be listed.

An overview table will be given presenting the frequencies and percentage of all participants with at least one TEAE by intensity, relationship to study intervention and seriousness, at least one TEAE leading to discontinuation of study intervention, and at least one TEAE of special interest.

The frequencies of participants with TEAEs will be summarized using MedDRA terms grouped by SOC and PT. Furthermore, the frequencies of participants with TEAEs will be summarized by intensity and by relationship to study intervention. In addition, the frequencies of participants with related TEAEs will be summarized by intensity.

Death, TESAEs, TEAESIs or TEAEs leading to discontinuation of study intervention will be listed separately and frequencies will be summarized, if applicable.

9.3.3.2 Other Safety Endpoints

Laboratory values, ECG parameters and vital signs will be summarized descriptively by parameter including changes from baseline. Arithmetic mean plots including standard deviation over time will be presented.

For laboratory values shift tables will be provided (by time point including any time point) focusing on the frequency and percentage of participants with shifts from within normal range (or below normal range) at baseline to above normal range post-baseline and from within normal range (or above normal range) at baseline to below normal range post-baseline. Courses of laboratory values out of normal range at least at one time point will be listed by parameter and treatment group (abnormal values will be flagged with ‘H’ for high and ‘L’ for low).

A frequency table will be provided for ECG findings (by time point including any time point).

9.3.4 Pharmacokinetic Analyses

Analysis of PK data will be reported in a separate M&S report, if applicable. However, the following statistics will be reported for plasma concentrations of zabedosertib at each visit (and time point if applicable): geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and geometric coefficient of variation (CV), arithmetic mean, standard deviation and CV, minimum, median, maximum value and the number of measurements as well as the number of measurements ≥ limit of quantification (LLOQ). Means at any visit will only be calculated if at least 2/3 of the individual data were measured and were above LLOQ. For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

9.3.5 Exploratory/Other Endpoint(s)

Exploratory endpoints will be analyzed using descriptive statistics and frequency tables. Details will be provided in the SAP.

9.3.6 Other Analyses

Other exploratory analyses may include the analyses of

- Correlation of efficacy data with weather and environmental data derived from outside this study setting.
    - It is considered to correlate disease activity parameters as assessed using the EASI, vIGA-AD, BSA affected by AD and Peak Pruitus 0-10 NRS with weather and environmental data derived from local weather stations (e.g., high pollen counts or specific weather situations such as dry/hot weather) on an exploratory basis. Results of this exploratory analysis, which will be stored and assessed in an external database, will be reported under a separate cover.

9.4 Interim Analysis

An interim analysis may be performed using the data of all study participants having either regularly completed or prematurely discontinued study intervention at a certain cutoff date, when a minimum of 80% of patients are evaluable. The eligibility of the respective study participants for the analysis sets will be checked and documented before unblinding for the interim analysis. Study intervention of participants not having completed the intervention period by the time of the interim analysis will not be unblinded. Access to the treatment codes of the participants included in the interim analysis prior to final database release will be restricted to an unblinded team, whereas the rest of the team remains blinded. No individual data of the interim analysis will be disclosed to the blinded study team responsible for further study conduct. Details of the measures to restrict access to unblinding data will be described in detail in a dedicated study blinding plan. The further study conduct or study design will not be affected by the results of the interim analysis. The final evaluation of study results will be performed as described in Section 9.4 and SAP.

Additionally, a blinded monitoring of sample size assumptions using methodology described in Friede et al, 2004 may be applied.

9.5 Sample Size Determination

A Bayesian concept will be used for inference, which is based on the posterior probability that the research hypothesis is true. Therefore, it is the goal of this study to demonstrate that zabedosertib is superior to placebo with posterior probability > 90%, i.e. $P(\pi_{BAY} > \pi_{Plac} \mid \text{data}) > 90\%$ (='clinical activity' criterion).

The EASI 75 responder rate of 0.49 for assumed systemic standard of care (SoC) dupilumab was derived as the mean responder rate from a meta-analysis on the active treatment arms in two Phase 3 AD studies (Simpson et al, 2017), comprising 919 participants.

Non-informative Beta(1,1) priors will be used for the Bayesian inference.
For Placebo, a response rate of 16% was assumed. The statistical power was determined with SAS 9.4.

Assuming that the EASI 75 responder rate in zabedosertib-treated participants is 0.49, evaluable data from 57 participants (38 on zabedosertib, 19 on placebo) will provide at least 90% power to establish superiority of zabedosertib. Approximately 72 participants will be randomly assigned to the study to obtain 57 evaluable participants overall (2:1 randomization zabedosertib versus placebo).

10 Supporting documentation and operational considerations

10.1.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.2 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted, reviewed and approved in accordance with national legislation and undergo scientific and ethical assessment before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.3 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Informed consent process

Detailed description of the recruitment strategy will be provided in country-specific documentation as required.

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Potential Participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Participants of skin biopsy sub-study will need to separately consent to participation.
- Participants providing photographs will need to separately consent to procedure.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF(s).

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5 Recruitment strategy

Not applicable.

10.1.6 Data protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the sponsor.
- The participants must be informed that they personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must

also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

- The participants must be informed that they medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7 Committees structure

Not applicable.

10.1.8 Dissemination of clinical study data

Bayer fulfills its commitment to publicly disclose study results through posting the result of the studies on public registries in accordance with applicable law and regulations.

Result Summaries of Bayer's sponsored clinical trials in drug development phases II, III and IV and Phase I studies in patients are provided in the Bayer Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

In accordance with the current EU regulation, result summaries will be submitted within one year from the end of the studies in adult populations or within 6 months for studies in pediatric population, in all participating countries. No preliminary data analysis (eg, on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study. Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) on or after January 01, 2014 as necessary for conducting legitimate research.

All Bayer-sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.9 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF and eCOA provider database unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.10 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Investigator Site File.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The following data will be the source and no additional source documentation will be available. These data are not needed for the participant's routine medical care.
  - Race (will be entered directly into the eCRF)
  - ECG data
  - ePRO data (study drug exposure data excluded)
  - ClinRO data
  - IRT (site-specific source identification list is maintained at the Investigator Site File)
  - Central laboratory data

10.1.11 Study and site start and closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants. The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate therapy and/or follow-up.

10.1.12 Publication policy

- The results of this study may be published or presented at scientific meetings by the sponsor. If this is foreseen by the investigator, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10–1 will be performed by the central laboratory (exception: dipstick urinalysis and pregnancy tests in urine). Detailed information about the collection, processing, storage and shipment of the samples will be provided separately in a laboratory manual.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing will be performed as detailed in Table 10–1.

Investigators must document their review of each laboratory safety report.

Table 10–1: Protocol-required safety laboratory assessments at visits V1 (screening), V3 (randomization), V 4 (Day 14), V5 (Day 28), V6 (Day 56), V7 (Day 84) and EOS (Day 112)

Hematology	White blood cell (WBC) count with differential	Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Platelet count	
	Red blood cell (RBC) count	
	RBC indices:	Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes
	Hemoglobin	
	Hematocrit	
	Coagulation	Prothrombin time (Quick) Activated partial thromboplastin time (aPTT) Fibrinogen International normalized ratio (INR)
Clinical chemistry[1]	Blood urea nitrogen (BUN)	
	Glucose (non-fasting or fasting) - only at screening and end of treatment	
	Creatinine	
	Urea	
	Uric acid	
	Total protein	
	Albumin	
	Alpha-acid glycoprotein (AGP)	
	High sensitivity C reactive protein (hsCRP)	
	Creatine kinase (CK)[2]	
	Electrolytes	• Sodium • Potassium • Calcium • Chloride
	Liver tests	• Total bilirubin • Direct bilirubin • Aspartate aminotransferase (AST/SGOT) • Alanine aminotransferase (ALT/SGPT) • Gamma-glutamyl transferase (GGT) • Alkaline phosphatase (AP) • Lactate dehydrogenase (LDH)
	Lipid profile (fasting[4]) - only at randomization and end of treatment	• Low-density lipoprotein (LDL) • High-density lipoprotein (HDL) • Total Cholesterol • Triglycerides (TGL)
Routine urinalysis	Dipstick test (local)	pH, glucose, protein, blood, ketones, leukocytes, nitrite
	Urinalysis)	Urinalysis including myoglobin and sediment, only if CK elevation > 5 x ULN was confirmed and other causes such as physical exercise are excluded (central lab preferred)
	Microscopic examination at central laboratory (only if blood or protein is abnormal in dipstick test)	
Pregnancy test	Urine and serum hCG pregnancy test (as needed for women of childbearing potential) [3]	
Other tests	At screening or randomization (if screening is not available) and EOT:	Total immunoglobulin E (IgE)
	At screening and EOT:	Estimated glomerular filtration rate (eGFR; MDRD formula)
	Only at screening:	Hepatitis B: Hepatitis B surface antigen (HBsAg), Anti-Hepatitis B core antibody (HBcAb), Hepatitis B surface antibody (HBsAb) Hepatitis C: (Hep C antibody) Human immunodeficiency virus (HIV) 1 and 2 Tuberculosis test (QuantiFERON GOLD Plus test)
	At visit 2 and if clinically indicated:	SARS-CoV-2 RNA test (real time-PCR, test specimen according to test recommendation)

For footnotes, see next page.

Footnotes to Table 10–1

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7. All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[2] Lab follow up includes:

- Serum: CK (incl. isoforms), creatinine, urea nitrogen, uric acid and calcium, potassium, phosphate, Prothrombin time (PT)
- Urine: urinalysis incl. myoglobin and sediment.

[3] Local urine testing (pregnancy test and dipstick urinalysis) will be standard for the protocol unless serum testing is indicated by the SoA or required by local regulation or IRB/IEC.

[4] If the participant arrives in a non-fasting state, the blood sample should be obtained and indicated in the CRF as non-fasting.

10.2.1 Guidance for management of muscle symptoms and CK elevations

If confirmed CK elevation > 5 fold ULN and other causes such as exercise are excluded, lab follow up and management according to the guidance for management of muscle symptoms and CK elevations as described in this section should be followed.

- Lab follow up (central lab analysis preferred) includes:
  - Serum: CK (incl. isoforms), creatinine, urea nitrogen, uric acid and calcium, potassium, phosphate, Prothrombin time (PT), thyroid stimulating hormone (TSH)
  - Urine: urinalysis incl. myoglobin and sediment.

- Throughout the study, subjects should be instructed to promptly report unexplained muscle pain or weakness, particularly if associated with malaise or fever. If this occurs, CK should be measured as soon as possible.
- If CK is found to be elevated ≥ 5 x ULN on routine testing, the subject should be questioned about muscle symptoms and re-tested within 3 days.
- A suitably-experienced physician should be involved in deciding appropriate management for the subject. The physician should be alerted to the occurrence of unexplained muscle symptoms, and any CK values ≥ 5 x ULN and must take immediate action if CK > 10 x ULN.
- For CK > 10 x ULN (confirmed, 2nd sample required) with or without muscle symptoms, discontinue study drug.
- For CK > 5 - 10 x ULN (confirmed, 2nd sample required)
  - If symptomatic and no alternative explanation exists, withhold therapy.
  - If symptomatic, or if symptomatic but alternative explanation exists, follow symptoms and CK level weekly until there is no longer medical concern or symptoms worsen and meet criteria above
- The following questioning and follow-up investigations should be performed:
  - Clarify the nature, duration and intensity of relevant symptoms
  - Clarify and document whether the patient was taking study treatment at the time of the event, or when the last done of study treatment was taken. Document dosing information in source and report if appropriate (e.g., if considered an SAE).

- Review possible predisposing factor, such as: unaccustomed exercise (including decorating, gardening, etc.), heavy alcohol intake, viral illness or severe bacterial infections (consider performing serology), concomitant medications (e.g., anesthetics, cholesterol-lowering agents – niacin, clofibrate, statins, ezetimibe, glucocorticoids, narcotic, chloroquine etc.) and consider diagnosis of other conditions which can cause myopathy (e.g. trauma).
  - → Physical examination for muscle tenderness, weakness and rash
  - → Measure lab parameters (as described above) within a few days
  - → Arrange to review the participant again in 4 to 10 days, or if symptoms of myopathy appear or worsen, or if the urine becomes very dark

- Myopathy is defined as muscle aches or weakness in association with CK increased to > 10 x ULN. If myopathy occurs or if on clinical grounds, statin-induced myopathy is diagnosed or suspected, statin therapy should be discontinued. Myopathy should always be recorded as an adverse event, and the Bayer representative must be informed.
- If the study treatment is temporarily disrupted, it is suggested that the Bayer representative be consulted before restarting study treatment.
- The Bayer representative should be consulted prior to permanently withdrawing a participant.

10.3 Appendix 3: Adverse events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended,

are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.

- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Sign, symptoms, or the clinical sequelae of suspected medication errors, misuse and abuse of either study intervention or a concomitant medication. Medication errors, misuse and abuse per se will not be reported as an AE/SAE, unless it is resulting in AE/SAE. Such medication errors, misuse and abuse should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets the one or more of the criteria listed:

a. **Results in death**

b. **Is life threatening**

- The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

f. **Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:
  - Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to

the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the sponsor's pharmacovigilance department.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are considered WOCBP (fertile)

1. Following menarche
2. From the time of menarche until becoming premenopausal unless permanently sterile (see below):
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 IU/L is required.
        - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
    - Permanent sterilization methods (for the purpose of this study) include:
        - Documented hysterectomy
        - Documented bilateral salpingectomy
        - Documented bilateral oophorectomy
        - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:

a) Documented hysterectomy

b) Documented bilateral salpingectomy

c) Documented bilateral oophorectomy

d) For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 IU/L is required.
    - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

Collection of pregnancy information:

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study-pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Skin biopsy assessment (substudy)

Skin barrier dysfunction is the initial step in the development of AD. Pharmacodynamic biomarkers will be evaluated in samples collected before and during treatment in order to determine the impact of the study intervention on these biomarkers.

- Participants will be offered a possibility to participate in an optional skin biopsy. In this study a molecular analysis of BMs will be performed.
- The participation in the substudy is voluntary and has no influence on the participation in the main study
- Skin biopsies will be taken at defined time points during the study as specified in the SoA
- Skin biopsies should be taken from the same lesion, if possible. Otherwise, a similar location should be selected.
- Candidate pharmacodynamic biomarkers in the skin biopsies may give hints to drug efficacy and may include (but are not limited to) for example:
- Biomarkers which may be related to the mode-of-action or are likely correlated with treatment effects - such as markers of inflammation (e.g., cytokines: IL-1β, IL-4, IL-33, TSLP, chemokines such as CCL17), epidermal hyperplasia (e.g., Ki67, keratin 16) and epidermal barrier markers (e.g., filaggrin).
- Skin epithelial height, markers of keratinocyte proliferation K16 (keratin 16) and Ki6-7 (optional analysis)

The results of the gene expression analysis of the skin biopsies may be reported separately (e.g., in a Biomarker Evaluation Report).

10.6 Appendix 6: Prohibited medications

Medications listed in Table 10–2 should be omitted 1 week before randomization visit and throughout the study. Please note that this is not an exhaustive list. See also in-/exclusion criteria in Sections 5.1 and 5.2.

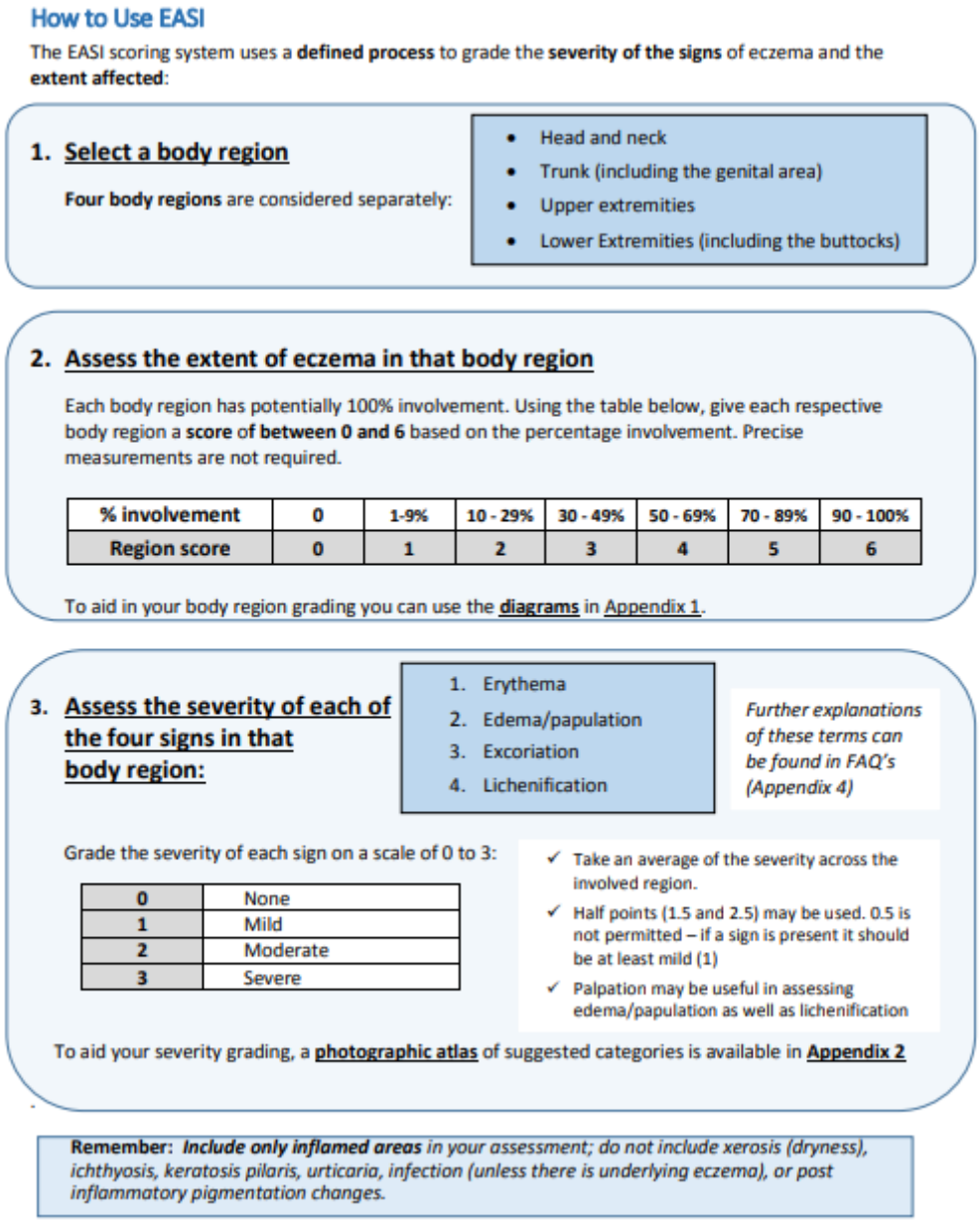
Table 10–2: Substrates (X) for breast cancer resistance proteins (BCRP) and organic-anion-transporting polypeptides (OATP) 1B1 and 1B3

Drug	BCRP	OATP 1B1	OATP 1B3
Ambrisentan	-	X	X
Asunaprevir	-	X	X
Atorvastatin	X	X	X
Bosentan	-	X	X
Cerivastatin	-	X	X
Cimetidine	-	-	-
Daunorubicin	X	-	-
Docetaxel	-	-	X
Donoprevir	-	X	X
Ezetimibe	-	X	-
Fexofenadine	-	X	-
Fluvastatin	X	X	X
Gadoxetic acid	-	X	X
Gefitinib	X	-	-
Glibenclamide	-	X	X
Hymecromone	X	-	-
Imatinib	X	-	-
Irinotecan	X	-	-
Lapatinib	X	-	-
Mitoxantrone	X	-	-
Nateglinide	-	X	X
Nitrofurantoin	X	-	-
Paclitaxel	-	-	X
Pibrentasvir	X	-	-
Pitavastatin	X	X	X
Prazosin	X	-	-
Pravastatin	-	X	X
Repaglinide	-	X	-
Revefenacin	-	X	X
Rifampicin	X	-	-
Rosuvastatin	X	X	X
Simeprevir	-	X	X
Simvastatin	X	X	-
Sulfasalazine	X	-	-
Sunitinib	X	-	-
Topotecan	X	-	-
Vincristine	X	-	-
Zidovudine	X	-	-

10.7 Appendix 7: Questionnaires

10.7.1 ClinROs scoring

10.7.1.1 Eczema Area and Severity Index (EASI)



How to Use EASI

The EASI scoring system uses a **defined process** to grade the **severity of the signs** of eczema and the **extent affected**:

1. Select a body region

Four body regions are considered separately:

- Head and neck
- Trunk (including the genital area)
- Upper extremities
- Lower Extremities (including the buttocks)

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a **score of between 0 and 6** based on the percentage involvement. Precise measurements are not required.

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

To aid in your body region grading you can use the **diagrams** in Appendix 1.

3. Assess the severity of each of the four signs in that body region:

1. Erythema
2. Edema/papulation
3. Excoriation
4. Lichenification

Further explanations of these terms can be found in FAQ's (Appendix 4)

Grade the severity of each sign on a scale of 0 to 3:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved region.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)
- ✓ Palpation may be useful in assessing edema/papulation as well as lichenification

To aid your severity grading, a **photographic atlas** of suggested categories is available in **Appendix 2**

Remember: ***Include only inflamed areas*** *in your assessment; do not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or post inflammatory pigmentation changes.*

easi-user-guide-dec-2016-v2.pdf (homeforeczema.org)

The assessed parameters are inserted into Figure 10–1. The final EASI score ranges from 0-72.

Figure 10–1: EASI scoring table

Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	+)	x	x 0.1	
Trunk	(+	+	+	+)	x	x 0.3	
Upper extremities	(+	+	+	+)	x	x 0.2	
Lower extremities	(+	+	+	+)	x	x 0.4	
The final EASI score is the sum of the 4 region scores							——— (0-72)

10.7.1.2 Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)

The clinicians are asked to select that vIGA-AD score that best describes the overall appearance of the lesions at a given point in time. The scale's morphology descriptors are nonoverlapping, noncomparative categories with "clear" skin representing the absence of disease and focus given to having clearly distinct categories for ratings of "mild" versus "almost clear". A decrease in the vIGA-AD score relates to an improvement in signs and symptoms.

Instructions:

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

Figure 10–2: COA instrument: vIGA-AD

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

Notes:
1. In indeterminate cases, please use extent to differentiate between scores.
For example:
• Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered “3 – Moderate”.
2. Excoriations should not be considered when assessing disease severity.

Validated-Investigator-Global-Assessment-Scale_vIGA-AD_2017.pdf (eczemacouncil.org)

10.7.1.3 Assessment of body surface area (BSA) affected by atopic dermatitis

Body surface area affected by AD will be assessed for each section of the body, using the “rule of nines”. The possible highest score for each region is:

Head and neck: 9%
Anterior trunk: 18%
Back: 18%
Upper limbs: 18%
Lower limbs: 36%
Genitals: 1%.

It will be reported as a percentage of all major body sections combined.

Before the start of the study at the individual site, all investigators will be trained on the correct assessment of BSA.

10.7.2 PROs scales and questionnaires

Figure 10–3: Peak Pruritus 0-10 NRS

On a scale of 0 to 10, with 0 being ‘no itch’ and 10 being ‘worst itch imaginable’, how would you rate your itch at the worst moment during the previous 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No itch										Worst itch imaginable

10.8 Appendix 8: Country-specific Requirements

10.8.1 France (FRA)

10.8.1.1 FRA-1: Country-specific requirements for France only

Amendment France - FRA-1 (15 FEB 2023)

This local amendment was prepared for France to address the country-specific changes requested by the local ethics committee (EC) in France Comité de Protection des personnes Ouest IV. The requested change only affects one inclusion criterion which was specified according to the French Public Health Code to further clarify exclusion of vulnerable persons in France.

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

This section implements country-specific modifications to the original protocol version 1.0, dated 08 JUL 2022, to meet local requirements in France.

Overview of changes

A description of changes and a brief rationale is provided in the table below:

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion criteria	Text added to inclusion criterion 8 to exclude vulnerable persons according to the French Public Health Code (persons referred in Articles L1121-5 to L 1121-8-1 and L1122-1-2, viewed on 10 FEB 2023).	As per French local EC (Comité de Protection des personnes Ouest IV) request

Changes to the protocol

Section 5.1 Inclusion criteria

[…]

8. Capable of giving signed informed consent as described in Section 10.1.4, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol and are not falling under the definition for vulnerable persons according to the French Public Health Code (persons referred in Articles L1121-5 to L 1121-8-1 and L1122-1-2, viewed on 10 FEB 2023) as follows:

- pregnant women, parturient and breastfeeding women
- deprived of their liberty by a judicial or administrative decision
- undergoing psychiatric care and people admitted to a health or social institution for purposes other than research
- adults subject to a legal protection measure or unable to express their consent.
- minors
- persons who are not affiliated to a social security scheme or beneficiary of such a scheme
- persons deceased or brain-dead (listed for completeness)

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