ALMIRALL, S.A.

Clinical Trial Protocol M-17923-33

Clinical Trial Protocol Title:	A Phase 3b, Open-label Study to Evaluate the Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis
Short Protocol Title:	Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis
Study Name	ADhope
Investigational Medicinal Product(s):	Lebrikizumab
Indication:	Moderate-to-severe atopic dermatitis
Development Phase:	Phase 3b
Final Protocol Version Date:	3.0, 29 July 2024
Amendment(s)	**Number:** 1 **Date:** 18 September 2023 2 29 July 2024
EU Trial Number:	2023-505558-16
Sponsor:	Almirall, S.A. Ronda General Mitre, 151 08022 Barcelona, Spain

Protocol Amendment Summary of Changes

Amendment / Version	Date	Description of Changes	Rationale
Version 1.0	08 May 2023	Original protocol	
Amendment 1 / Version 2.0	18 Sep 2023	The dosing paradigm is not changed, but the language has been revised throughout.	To provide clarity on dosing
		Visit Days in the Schedule of Assessments (Table 1) has been revised	To provide clarity on the visit schedule and windows for the visit
		Trial design schematic (Figure 1) has been revised	To provide clarity on the study design and dosing
		Section 7.2.2, has been revised with information on prior lebrikizumab treatment in dupilumab-experienced patients	Limited data from the ADhere study support the collection of additional efficacy and safety data in patients previously treated with dupilumab
		Exclusion criterion 5 has been revised	To provide clarity on the exclusion of patients with prior infections
		Exclusion criteria 6, 7, and 8 have been revised	To provide clarity on the exclusion of patients with viral hepatitis infection, cirrhosis/hepatitis, or endoparasitic infections
		Exclusion criterion 11 has been revised	To provide clarity on the exclusion of patients due to laboratory abnormalities
		Section 8.4.2 has been revised specifying the treatment discontinuation due to lack of effectiveness is per the Investigator's judgement	To provide guidance on treatment discontinuation
		Sections 9.2 and 9.3 have been revised with regard to personnel receiving study drug at the sites	To remove redundancy and clarify the Investigator, pharmacist, or designee may be responsible for receiving drug at the study site
		In Section 9.9.2 and Table 3, the washout period for dupilumab has been extended to 8 weeks	Based on the pharmacology of dupilumab and in line with prior lebrikizumab protocols
		In Section 10.1, procedures for informed consent have been revised	To provide clarity on procedures for obtaining informed consent
		In Section 10.6.1, it is no longer required that AESIs be reported separately to the Pharmacovigilance group	AESIs and additional data for these events will be captured as with all other AE, including additional data, unless they meet criteria for seriousness.
		Section 11.1 has been updated with the rationale for the 60% response rate used in the sample size estimation	To provide clarity on the basis for the expected response rate
		Section 11.2 has been revised specifying that the SAP will be prepared prior to first patient enrolment, rather than database lock	For an open-label study, this is recommended to avoid bias

Amendment / Version	Date	Description of Changes	Rationale
Amendment 2 / Version 3.0	29 Jul 2024	Synopsis and Section 6.1, the number of clinical endpoints has been reduced.	To provide focus on the most clinically relevant study endpoints. All additional endpoints will be defined within the SAP.
		Table 1 and Section 10.4.10, Investigator-reported CCI is removed.	CCI is assessed only by the study participant.
		Additional information is provided in the Synopsis on the use of concomitant medications and the trial population.	These additions to the Synopsis do not reflect changes to the design and are implemented only for clarity on the study conduct.
		Section 17.1, The Ebglyss® Summary of Product Characteristics (SmPC) replaces the Investigator's Brochure as the clinical reference document for lebrikizumab.	European marketing authorisation was granted for lebrikizumab on 16 November 2023 (EMEA/H/C/005894) for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy. In this study, lebrikizumab is used within the scope of this authorisation, thus the approved SmPC serves as the clinical reference document.
		Section 10.6.5, the reference safety information for assessment of expectedness is defined as Section 4.8 of the SmPC.	In accordance with CTR 536/2014
		The definition of inpatient hospitalisation for SAE determinations is revised in Section 10.6.1.	In accordance with recent guidance on CTR 536/2014.
		Synopsis and Section 11.11, interim analysis may be performed when approximately 100 participants have completed Week 24.	Clarification on the timing of the interim analysis.
		Minor editorial and administrative changes.	For clarity, correctness, and consistency.

Sponsor Signatures

Clinical Trial Protocol Title: A Phase 3b, Open-label Study to Evaluate the Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis

Trial Code: M-17923-33

The individuals signing this clinical trial protocol declare that they have reviewed it for completeness, accuracy. They are responsible for the trial and agree to conduct it in adherence to the present document, any amendments, to International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, European Union (EU) Clinical Trial Regulation No 536/2014, and to local regulatory requirements, wherever applicable.

Sponsor

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona, Spain

Functional Role	Name	Signature
International Clinical Trial Manager	PPD	PPD
Statistician	PPD PPD	PPD
Global Clinical Lead	PPD	PPD

Coordinating Investigator Signature

Clinical Trial Protocol Title:	A Phase 3b, Open-label Study to Evaluate the Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis
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Coordinating Investigator

Role	Name	Signature
Coordinating Investigator	PPD	PPD

Principal Investigator Signature

Clinical Trial Protocol Title:	A Phase 3b, Open-label Study to Evaluate the Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis
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Principal Investigator

Role	Name	Signature	Date
Principal Investigator			

1 Protocol Synopsis

Title:

A Phase 3b, Open-label Study to Evaluate the Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis

Short Title:

Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis

Investigators:

A Principal Investigator will be designated at each participating clinical trial centre and a Coordinating Investigator will be nominated among the participating sites. The name, address, and affiliation of each Principal Investigator and the Coordinating Investigator will be detailed in the final clinical trial report.

Trial Centre(s):

The trial is planned to be conducted in multiple study centres in Germany, the United Kingdom, and the Netherlands.

Trial Duration:

The duration of the entire trial from first participant, first visit to last participant, last visit is anticipated to be approximately 20 months.

Phase of Development:

This is a Phase 3b trial.

Rationale:

Atopic dermatitis (AD) is a chronic, inflammatory, skin disorder characterised by recurrent eczematous lesions, intense itch, and skin pain (eg, discomfort or soreness). The ubiquitous presence of IL-13 in the skin of patients with AD supports the evaluation of anti-IL-13 therapies in patients with AD. Lebrikizumab is an immunoglobin (Ig) G4 monoclonal antibody (mAb) that binds with high affinity and slow off-rate to IL-13 and selectively inhibits IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/IL-13 receptor alpha-1 (IL-13Rα1) pathway, thereby blocking the downstream effects of IL-13 with high potency. Lebrikizumab-bound IL-13 can still bind IL-13 receptor alpha-2 (IL-13Rα2), allowing subsequent internalization and natural clearance of IL-13. Blockade of IL-13 signalling is expected to be of benefit in diseases in which IL-13 is a central cytokine to the disease pathogenesis, such as AD.

Two identically designed, pivotal Phase 3 placebo-controlled clinical trials (J2T-DM-KGAB, hereafter "ADvocate 1" and J2T-DM-KGAC, hereafter "ADvocate 2") demonstrated the efficacy and safety of lebrikizumab 250 mg administered every other week (Q2W) for 16 weeks as monotherapy in adult and adolescent patients with moderate-to-severe AD, and a third pivotal, placebo-controlled Phase 3 trial (J2T-DM-KGAD, hereafter "ADhere") demonstrated the efficacy and safety of lebrikizumab 250 mg Q2W administered for 16 weeks

in combination with topical corticosteroid (TCS) treatment. Data from lebrikizumab-treated participants who achieved clinical response (Investigator Global Assessment [IGA] of 0 or 1 or 75% reduction in Eczema Area and Severity Index [EASI] from baseline) at week 16 without the use of rescue therapy and continued treatment in ADvocate 1 or ADvocate 2, as well as participants from ADhere who continued treatment in a separate long-term protocol (J2T-DM-KGAA, hereafter "ADjoin"), showed that the treatment effects achieved at week 16 could be equally well maintained up to 52 weeks by the administration of lebrikizumab 250 mg either Q2W or every fourth week (Q4W).

This Phase 3b study seeks to evaluate clinical aspects of lebrikizumab treatment beyond those previously tested in the pivotal studies. Specifically, the study will examine the effectiveness and safety of lebrikizumab in a patient population with more moderate AD, the effectiveness and safety of lebrikizumab in patients previously treated with dupilumab, clinical responses to lebrikizumab Q4W dosing beginning at week 16, and the impact of lebrikizumab treatment on AD in areas of the body that are difficult to treat. Furthermore, the study will provide insights into CCI that may be affected by lebrikizumab treatment.

Objectives and Endpoints:

Objectives	Endpoints
Primary Objective	
To evaluate the effectiveness of 24 weeks of lebrikizumab in improving disease severity, signs, and symptoms in adults and adolescents with moderate-to-severe AD	**Primary Endpoint** • Percentage of participants achieving EASI score ≤7 at Week 24 **Secondary Endpoints** • Percentage of participants achieving EASI score ≤7, EASI ≤5, and EASI ≤3 by visit • Percentage of participants achieving EASI 75 and EASI 90 by visit • Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points by visit • Percentage of participants achieving SCORAD 75 and SCORAD 90 by visit • Percentage change from baseline in mTLSS (hands) from baseline by visit CCI
Secondary Objectives	
To evaluate the impact of 24 weeks of lebrikizumab treatment on patient-reported and Investigator-reported outcome measures in adults and adolescents with moderate-to-severe AD	**Secondary** *Pruritus* • Percentage of participants with Pruritus NRS ≥4 at baseline achieving ≥4-point improvement in Pruritus NRS from baseline by visit *Quality of Life* • Percentage of participants achieving DLQI 0-1 by visit • Percentage of participants with DLQI ≥4 at baseline achieving ≥4-point improvement in DLQI from baseline by visit • Percentage of participants achieving cDLQI 0-1 by visit • Percentage of participants with cDLQI ≥6 at baseline achieving ≥6-point improvement in cDLQI from baseline by visit

Objectives	Endpoints
	Sleep Loss Due to Itch • Percentage of participants with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least 2-point reduction by visit *Disease Control* • Percentage of participants with POEM ≥4 at baseline achieving ≥4-point improvement in POEM from baseline by visit CCI [redacted]
Safety Objectives	
To evaluate the safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD	• Percentage of participants with treatment-emergent AEs including SAEs, related AEs, and AEs leading to study treatment discontinuation, and AESIs
CCI [redacted]	

Abbreviations: AD=atopic dermatitis; AE=adverse event; AESI=adverse event of special interest; BSA=body surface area; cDLQI=Children's Dermatology Life Quality Index; DQLI= Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI 75/90=75% or 90% reduction in EASI from baseline; mTLSS=modified Total Lesion Symptom Score; POEM=Patient Oriented Eczema Measure; Pruritus NRS=Pruritus Numerical Rating Scale; SAE=serious adverse event; SCORAD=Scoring Atopic Dermatitis; SCORAD 75/90=75% or 90% reduction in SCORAD from baseline; CCI [redacted]

Trial Design:

This is a single arm, open-label, Phase 3b study evaluating the effectiveness and safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD. The study will enrol approximately 240 participants.

Participants will be screened for study entry within 4 weeks of study Day 1. For eligible participants, loading doses of lebrikizumab 500 mg subcutaneous (SC) injection will be administered by site personnel at Day 1 and Week 2. Beginning at Week 4, lebrikizumab 250 mg will be administered Q2W, and participants will have the option of self-administration, following training of the participant and/or caregiver, or the participant may continue to receive injections at the study site. Beginning at Week 16, the dosing frequency will be reduced to every 4 weeks, and participants will receive lebrikizumab 250 mg SC injection Q4W up to Week 24.

Lebrikizumab monotherapy is recommended, but the concomitant use of topical corticosteroids (TCS) is permitted, per the Investigator's discretion, for participants on a stable low or mid-potency TCS regimen at baseline. Intermittent use of other topical medications (eg, topical

calcineurin inhibitors [TCIs] and phosphodiesterase-4 [PDE4] inhibitors) is permitted for the treatment of worsening AD symptoms during the trial. Participants who may require short-term systemic corticosteroid treatment for symptoms of AD will be assessed on a case-by-case basis. The concomitant use of other immunosuppressive/immunomodulating drugs for AD, including long-term systemic corticosteroids use (>30 days), is prohibited. CCI [redacted]

Participants will undergo final study assessments at Week 24, ie, 4 weeks after the last dose of study medication at Week 20. For participants who withdraw from the study prior to Week 24, a safety follow-up visit will take place 4 weeks after the last dose of study medication.

Number of Participants:

A sufficient number of patients with moderate-to-severe AD will be screened to enrol approximately 240 study participants.

Enrolment will be controlled to ensure representation from each of the participating countries.

Trial Population:

The study will enrol adults and adolescents (aged ≥12 to <18 years and weighing ≥40 kg) with moderate-to-severe AD for at least 1 year, a history of inadequate response to topical treatment, and who are candidates for systemic therapy. At baseline, participants must have an EASI score ≥12, an IGA score ≥3, and ≥10% body surface area (BSA).

The study will be enrolled such that up to 20% of all participants will have had prior exposure to dupilumab, including those with suboptimal responses.

Test Investigational Medicinal Product, Dosage, and Mode of Administration:

Substance code/name:	Lebrikizumab
Administration route	SC injection
Unit dose/strength:	Lebrikizumab 250 mg will be provided as a solution for injection in a pre-filled syringe (PFS). Each single-use PFS contains 250 mg of lebrikizumab in 2 mL solution (125 mg/mL)
Dosage form:	Solution for injection
Frequency	At Day 1 and Week 2, loading doses of lebrikizumab 500 mg (2 injections) will be administered. Beginning at Week 4, lebrikizumab 250 mg (1 injection) will be administered Q2W up to Week 16. Beginning at Week 16, lebrikizumab 250 mg (1 injection) will be administered Q4W up to Week 24.

Reference Investigational Medicinal Product, Dosage, and Mode of Administration:

Not applicable.

Methodology:

Trial visits and assessments will be performed in accordance with the Schedule of Assessments (Table 1).

Duration of Treatment:

The duration of each participant's treatment is 24 weeks.

Duration of Participation in the Trial:

The total duration of each person's participation in the trial, including screening and treatment is estimated at 28 weeks (4-week Screening Period + 24-week Treatment Period).

Statistical Methods

Sample Size Calculation

CCI [redacted]

Analysis Populations

The following analysis sets are defined:

- The Full Analysis Set (FAS) includes all enrolled participants.
- The Safety Analysis Set (SAF) includes all enrolled participants who received at least 1 dose of the study drug.

The analysis of all effectiveness and patient- and Investigator-reported outcome variables will be performed on the FAS. All safety and CCI [redacted] will be conducted using the SAF.

Statistical Analysis

Full study results will be delivered once all participants have completed the study (Week 24) or discontinued from the study prior to this point.

All effectiveness, patient- and Investigator-reported outcome, safety, and CCI [redacted] endpoints will be summarised by means of descriptive statistics. Methods for handling missing data will be described in the Statistical Analysis Plan (SAP). Any additional CCI [redacted] will be described in a separate Exploratory Data Analysis Plan for CCI [redacted]

The number and percentage of participants with treatment-emergent adverse events (AEs), serious adverse events (SAEs), related AEs, AEs leading to study treatment discontinuation, and adverse events of special interest (AESIs) will be summarised.

Subgroup analyses include but are not limited to prior exposure to dupilumab (yes/no), baseline disease severity (EASI score), and country.

Interim Analysis

Some effectiveness variables (eg, modified Total Lesion Symptom Score [mTLSS]) and outcome measures (eg, CCI [redacted] included in this protocol have not been previously evaluated in patients treated with lebrikizumab. In order to gain a preliminary understanding of these measures in lebrikizumab-treated patients, an interim analysis may be performed when approximately 100 participants have completed Week 24 (ie, based on a data cut-off). The interim analysis will only be performed if relevant clinical information may be gained in a timely manner prior to the completion of the full study, based on the study recruitment rate.

Table 1 Schedule of Assessments

Study Procedures	Screening	Treatment Period					SFU[a]
Visit Number	1	2	3	4	5	6	
Study Week (W)		W0	W2	W4	W16	W24	
Study Day(s) ± window[b]	Day -28 to Day -1	Day 1 (Baseline)	Day 14±3d	Day 28±3d	Day 112±5d	Day 168±7d	+7d
Informed consent/assent form	X						
Fitzpatrick scale	X						
Inclusion and exclusion criteria	X	X					
Demographics and medical history	X	X					
Enrolment		X					
Physical examination, height[c], weight	X					X	
Haematology, chemistry	X					X	X
Pregnancy test and contraception check[d]	X	X		X	X	X	X
AEs	←	—	—	—	—	→	X
Prior and concomitant medications/therapies	←	—	—	—	—	→	X
Dispense/return eDiary[h]	X					X	X
Train, check understanding, and recording of data in the eDiary	←	—	—	—	—	→	
IGA, CCI EASI, BSA[m]	X	X	X	X	X	X	
Pruritus NRS[e]	←	—	—	—	—	→	
SCORAD		X	X	X	X	X	
Sleep-Loss Scale[j,k]	X	X	X	X	X	X	
DLQI or CDLQI[k]		X	X	X	X	X	
POEM[k]		X	X	X	X	X	
Modified Total Lesion Symptom Score (mTLSS) for hands[n]		X	X	X	X	X	
CCI	CCI						

Study Procedures	Screening	Treatment Period					SFU[a]
Visit Number	1	2	3	4	5	6	
Study Week (W)		W0	W2	W4	W16	W24	
Study Day(s) ± window[b]	Day -28 to Day -1	Day 1 (Baseline)	Day 14±3d	Day 28±3d	Day 112±5d	Day 168±7d	+7d
CCI							
CCI	CCI						
CCI							
Administer study drug[i]		←	—	—	—	→	
Training on self-administration[i]				X			
Dispense study drug for self-administration[i]				X	X		
Product Complaint reporting		←	—	—	—	→	
Assess treatment compliance[f]			X	X	X	X	X
Genomic sampling[g]		X					
CCI	CCI						

Abbreviations: AE=adverse event; BSA=body surface area; CDLQI=Children Dermatology Life Quality Index; d=day; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; eDiary=electronic diary; hCG=human chorionic gonadotropin; IGA=Investigator's Global Assessment; mTLSS=modified Total Lesion Symptom Score; CCI POEM=Patient-Oriented Eczema Measure; Pruritus NRS=Pruritus Numerical Rating Scale; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous; SCORAD=Scoring Atopic Dermatitis; SFU=Safety Follow-up; TCS=topical corticosteroids; CCI W=week; WOCBP=women of child-bearing potential

a. Only for participants who withdraw from the study prior to W24, a SFU visit will take place 4 weeks after the last dose of study medication.
b. Visit window for patient-reported outcomes is -3 days for W2, then -5 days through W16, and -7 days for W24. The window for lebrikizumab self-administration is ±3 days from W4 up to W16 and then ±5 days from Week 16 up to W24.
c. Height need only be captured at screening.
d. Serum beta-hCG at Screening for WOCBP, and urine pregnancy testing at all other identified visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period. The contraception check is to confirm that contraception, if required, is used consistently and correctly.
e. Completed eDiary entries for Pruritus NRS are needed for a minimum of 4 out of 7 days in the week preceding Day 1/Baseline visit. Then Pruritus NRS to be performed daily up to W2, and weekly from W2 to W16, and every 2 weeks from W16 to W24.
f. Compliance assessment for study drug, as well as accountability. For participants who discontinue from the study, any unused medication to be returned at the SFU.
g. Samples for genomic testing will be collected from all consenting participants. A specific consent is required for genomic sampling.
h. Return of eDiary is applicable only if an electronic device is provided to the participant.

i. For eligible participants, loading doses of lebrikizumab 500 mg subcutaneous (SC) injection will be administered by site personnel at Day 1 and Week 2. Beginning at Week 4, lebrikizumab 250 mg will be administered Q2W, and participants will have the option of self-administration, following training of the participant and/or caregiver, or the participant may continue to receive injections at the study site. Beginning at Week 16, the dosing frequency will be reduced to every 4 weeks, and participants will receive lebrikizumab 250 mg SC injection Q4W up to Week 24 (ie, last Q4W dose administered at W20). For participants who choose to self-administer, sufficient study drug will be dispensed to the participant/caregiver at Weeks 4 and 16 to ensure adequate supplies until the next scheduled study visit.

j. Completed eDiary entries for Sleep-Loss Scale are needed for a minimum of 4 out of 7 days in the week preceding Day 1/Baseline visit. Then the Sleep-Loss Scale is to be performed daily up to W2, weekly from W2 to W16, and every 4 weeks from W16 to W24.

k. Patient-reported outcomes and quality of life measurements should all be completed before other study assessments. Assessments/procedures are recommended to be conducted in the following order: 1) patient-reported outcomes; 2) Investigator assessments and other effectiveness assessments, 3) safety and laboratory assessments, 4) blood sampling for genomics and CCI , and 5) administration of study drug.

l. CCI [redacted]

m. CCI [redacted]

n. mTLSS to be performed only for patients with AD of the hands at Day 1/Baseline

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3 List of Abbreviations

AD	Atopic dermatitis
AE	Adverse event
AESI	Adverse event of special interest
ALCOA+	Attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available
BMI	Body mass index
BSA	Body Surface Area
cDLQI	Children's Dermatology Life Quality Index
CI	Confidence interval
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CSR	Clinical study report
DLQI	Dermatology Quality of Life Index
DM	Data Management
DMP	Data Management Plan
DPO	Data Protection Officer
EASI	Eczema Area and Severity Index Score
EASI 75	75% reduction from baseline in the EASI score
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eDiary	Electronic diary
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IAF	Informed Assent Form
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IGA	Investigator's Global Assessment
IL	Interleukin
IL-13	Interleukin 13
IL-13Rα1	Interleukin 13 receptor alpha 1
IL-13Rα2	Interleukin 13 receptor alpha 2
IL-4Rα	Interleukin 4 receptor alpha
IMP	Investigational medicinal product
ISR	Injection site reaction
IV	Intravenous

JAK	Janus kinase
mAb	Monoclonal antibody
MCMC-MI	Markov Chain Monte-Carlo-multiple imputation
mTLSS	modified Total Lesion Symptom Score
PDF	Portable document format
POEM	Patient-Oriented Eczema Measure
PRO	Patient-Reported Outcome
Pruritus NRS	Pruritus Numerical Rating Scale
Q2W	Every other week
Q4W	Every 4 weeks
QoL	Quality of life
RNA	ribonucleic acid
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SFU	Safety follow-up
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TCS	Topical corticosteroids
Th	T helper
CCI	[redacted]
US	United States
WOCBP	Women of childbearing potential

4 Sponsor, Investigator(s) and Trial Administrative Structure

4.1 Sponsor

Almirall S.A. (legal entity)
Ronda General Mitre, 151
08022 Barcelona, Spain

4.2 Investigator(s)

A Principal Investigator will be designated at each participating clinical trial centre and a Coordinating Investigator will be nominated among the participating sites. The name, address, and affiliation of each Principal Investigator and the Coordinating Investigator will be detailed in the final clinical trial report (CSR).

4.3 Administrative Structure

Medical Expert appointed by the Sponsor for this trial:

PPD , MD
Global Clinical Lead
Late Stage Clinical Development
PPD

The roles and responsibilities of other staff involved in the conduct of this study from the Sponsor, Contract Research Organisation (CRO), and other vendors, will be defined in a separate document and updated, as appropriate, throughout the course of the study.

5 Introduction

Lebrikizumab is being developed for patients with moderate-to-severe atopic dermatitis (AD) inadequately controlled by topical therapies who are candidates for systemic therapy. A summary on the indication, mechanism of action, and completed nonclinical and clinical studies is provided below. A detailed description on the product identity and composition, clinical particulars including undesirable effects, and pharmacological and pharmaceutical properties of lebrikizumab is provided in the Ebglyss® Summary of Product Characteristics (SmPC).

5.1 Background Information

5.1.1 Indication

Atopic dermatitis is a chronic inflammatory skin disorder characterised by recurrent eczematous lesions and intense itch. The one-year prevalence of AD among adults is estimated between 2% and 7% in the United States (US), Europe, and Japan (Diepgen 2016, Harrop 2007, Sacotte 2018, Saeki 2006), and up to approximately 50% of adult patients suffer from moderate-to-severe disease (Barbarot 2018). Approximately 12% to 20% of children globally have AD (Hadi 2021, Hanifin 2007, Harrop 2007, Langan 2020, McKenzie 2019, Sacotte 2018,

Shaw 2011). Atopic dermatitis is the leading cause of the non-fatal disease burden conferred by skin conditions on a global level (Weidinger 2018), and in particular moderate-to-severe AD has a marked negative impact on quality of life (QoL) and places a tremendous burden on patients and societies (Drucker 2017, Weidinger 2016).

Atopic dermatitis commonly manifests in early childhood and shows diverse trajectory patterns, ranging from early life transient disease to relapsing remitting AD, chronic persistent AD, or long periods of remission followed by recurrence; for most patients AD is lifelong disease with variable expressivity (Langan 2020). Disease flares are unpredictable and can be caused by a multitude of factors such as exposure to environmental factors, irritants, and allergens (Weidinger 2016). Clinically, AD is characterised by typically poorly demarcated erythematous, sometimes violaceous to brownish scaly and sometimes oozing macules, papules, patches and/or plaques, often with excoriations and lichenification(Weidinger 2016). The dominant symptom of AD is intense itch (Weidinger 2016), which may lead to sleep disturbances (Galli 2020).

Pathophysiologically, AD is characterised by a complex skin barrier dysfunction with a profoundly altered skin microbiome and a cutaneous T-cell driven inflammation (Langan 2020, Weidinger 2018). Lesional skin shows an altered expression of genes related to keratinocyte activity and differentiation, as well as T cell infiltration and activity, with a striking upregulation of genes encoding T helper (Th) 2 cells associated proteins, in particular interleukin (IL)-13 (Leyva-Castillo 2020, Möbus 2021, Tsoi 2019). Interleukin-13 is thought to be the central mediator of cutaneous type 2 inflammation (Bieber 2020) and is involved also in early innate immune signalling (Halim 2016, Mayer 2021). In more chronic disease stages, Th1-mediated and Th17-mediated responses appear to be upregulated as well(Tsoi 2020). Type 2 cytokines, and in particular IL-13, not only drive inflammation through attraction and activation of T cells, eosinophils, and other immune cells, but also decrease the expression of epidermal structural and functional barrier proteins such as filaggrin, loricrin, and involucrin, and antimicrobial peptides, thereby compromising skin barrier function (Langan 2020, Weidinger 2018). The high abundance of IL-13 in the skin of patients with AD and its central role for type 2 skin inflammation support the evaluation of anti-IL-13 therapies in patients with AD.

5.1.2 Current Treatments

Atopic dermatitis management aims to improve signs, symptoms, and QoL, and to establish long-term disease control using a multi-stepped approach. The main principles are continuous epidermal barrier repair with emollients and anti-inflammatory therapy with topical corticosteroids (TCS, eg, hydrocortisone), topical calcineurin inhibitors (TCI, eg, tacrolimus), topical phosphodiesterase-4 (PDE4) inhibitors (eg, crisaborole), and topical Janus kinase (JAK) inhibitors (eg, ruxolitinib cream). When topical therapies are insufficient to treat signs and symptoms, systemic therapy is recommended. The effectiveness of many systemic immunosuppressive agents, both approved (eg, ciclosporin [(NEORAL 2021)]) and off-label drugs, used to treat AD is variable, and the duration of their use is limited due to (cumulative) toxicity (Wollenberg 2020). Newer biologic agents such as dupilumab, which targets the IL-4 receptor (IL-4R) (Dupixent SmPC), have shown robust efficacy and favourable tolerability (Simpson 2016), but there remains a need in AD for other therapies that can address the underlying key immunopathogenic process and improve the outcomes for patients (Langan 2020). Interleukin-13 is firmly established as the key cytokine of type 2 inflammation in the skin (Bieber 2020) and thus represents a prime therapeutic target. The recently approved anti-

IL-13 monoclonal antibody (mAb) tralokinumab (Adtralza SmPC) has shown good efficacy and safety (Wollenberg 2021). More recently, the oral reversible JAK inhibitors baricitinib, upadacitinib, and abrocitinib, which cause a broad cytokine inhibition, have been authorised for the treatment of moderate-to-severe AD in Europe (Cibinquo SmPC, Olumiant SmPC, Rinvoq SmPC). The JAK inhibitors have shown robust efficacy but a more complex safety profile for use in AD (eg, monitoring for lipids, liver enzymes, and haematology), as compared to approved biologics (Chen 2022, Silverberg 2021, Weidinger 2020).

Significant unmet medical needs remain because of the chronicity and heterogeneity of the disease, and a considerable proportion of patients show only limited or partial response or no response, lose response over time, or are intolerant to currently available systemic therapies (Narla 2022, Silverberg 2022, Silverberg 2021, Simpson 2017, Wollenberg 2021).

Lebrikizumab is a novel mAb against IL-13 with a mode of action that selectively prevents the formation of the IL-4 receptor alpha (IL-4Rα)/IL-13 receptor alpha-1 (IL-13Rα1) heterodimer receptor signalling complex, while still allowing signalling through the IL-13 receptor alpha-2 (IL-13Rα2) decoy receptor (Ratchataswan 2021).

5.1.3 Mechanism of Action

Lebrikizumab is an immunoglobulin (Ig) G4 mAb that binds with high affinity and slow off-rate to IL-13 and selectively inhibits IL-13 signalling through the IL-4Rα/IL-13Rα1 pathway, thereby blocking the downstream effects of IL-13 with high potency (Okragly 2021). Lebrikizumab-bound IL-13 can still bind IL-13Rα2 allowing subsequent internalization and natural clearance of IL-13 (Wulur 2021). Blockade of IL-13 signalling is expected to be of benefit in diseases in which IL-13 is a central cytokine to the disease pathogenesis, such as AD (Bieber 2020, Ratnarajah 2021).

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5.1.5 Clinical Studies

The clinical development program for lebrikizumab in AD included multiple Phase 2 and Phase 3 studies in patients with moderate-to-severe AD. The pivotal Phase 3 studies are summarised in Section 5.1.5.1.

5.1.5.1 Pivotal Studies

The primary evidence for the efficacy and safety of lebrikizumab comes from two identical pivotal Phase 3, randomised, double-blind, placebo-controlled trials of lebrikizumab as monotherapy in adults and adolescents (12 to <18 years and weighing ≥40 kg) with moderate-to-severe AD, J2T-DM-KGAB, hereafter "ADvocate 1" and J2T-DM-KGAC, hereafter "ADvocate 2." In addition, a third Phase 3 pivotal study J2T-DM-KGAD, hereafter "ADhere," demonstrated the efficacy and safety of lebrikizumab used in combination with TCS.

Study Designs

In ADvocate 1 (N=424) and ADvocate 2 (N=427), participants were randomised 2:1 to 250 mg lebrikizumab (loading dose of 500 mg given at weeks 0 and 2) or placebo by SC injection once every other week (Q2W). At week 16, participants achieving either Investigator Global Assessment (IGA) of 0 or 1 or a 75% reduction in Eczema Area and Severity Index (EASI) from baseline (EASI 75) without the use of rescue therapy were re-randomised 2:2:1 to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg every fourth week (Q4W), or matching placebo up to week 52.

In ADhere (N=211), participants were randomised 2:1 to either 250 mg lebrikizumab (loading dose of 500 mg given at weeks 0 and 2) or placebo administered by SC injection Q2W up to week 16. Topical corticosteroids were initiated at baseline in all participants and tapered or stopped, as needed, based on treatment response.

Efficacy Results

During the 16-week placebo-controlled period in the pivotal studies, lebrikizumab 250 mg Q2W demonstrated superiority to placebo (ADvocate 1 and ADvocate 2) or placebo+TCS (ADhere) across multiple outcome measures including skin inflammation related to AD, itch, and participant QoL. At week 16, a higher proportion of participants in the lebrikizumab arms achieved the co-primary endpoints, IGA 0 or 1 with ≥2-point improvement from baseline and EASI 75, and the differences with respect to placebo or placebo+TCS were statistically significant and clinically meaningful:

- The proportions of participants achieving IGA 0 or 1 with a ≥2-point improvement from baseline were 43.1% and 33.2% for lebrikizumab-treated participants and 12.7% and 10.8% for placebo participants in ADvocate 1 and ADvocate 2, respectively, for risk differences of 29.7% ($p<0.001$) and 21.9% ($p<0.001$), respectively, and in the ADhere study, 41.2% of lebrikizumab+TCS participants and 22.1% of placebo+TCS participants achieved IGA 0 or 1 with a ≥2-point improvement from baseline (risk difference of 18.3% [$p<0.05$]).
- The proportions of participants achieving EASI 75 were 58.8% and 52.1% for lebrikizumab-treated participants and 16.2% and 18.1% for participants in the placebo

groups in ADvocate 1 and ADvocate 2, respectively, for risk differences of 42.0% ($p<0.001$) and 33.3% ($p<0.001$), and in the ADhere study, 69.5% of lebrikizumab+TCS participants and 42.2% of placebo+TCS participants achieved EASI 75 (risk difference of 26.4% [$p<0.001$]).

Participants in ADvocate 1 and ADvocate 2 who were treated with lebrikizumab and achieved protocol-defined clinical response (IGA 0/1 or EASI 75) at week 16 without the use of rescue therapy, maintained higher response rates when continuing treatment with lebrikizumab 250 mg, either Q4W or Q2W, compared to those who switched to placebo (ie, participants withdrawn from lebrikizumab). A pooled analysis of these identical studies showed that, at week 52,

- 77% of lebrikizumab 250 mg Q4W and 71% of lebrikizumab 250 mg Q2W-treated participants maintained an IGA 0/1 response at Week 52, compared to 48% of participants in the placebo group (lebrikizumab withdrawal)
- 82% of lebrikizumab 250 mg Q4W and 78% of lebrikizumab 250 mg Q2W-treated participants maintained an EASI 75 response at Week 52, compared to 66% of participants in the placebo group (lebrikizumab withdrawal)

Similarly, participants in ADhere who were treated with lebrikizumab+TCS, achieved clinical response at week 16 (IGA 0/1 or EASI 75) and continued lebrikizumab treatment in the extension study J2T-DM-KGAA ("ADjoin") showed similar maintenance of clinical response, whether participants were treated Q2W or Q4W:

- 87% of lebrikizumab 250 mg Q4W+TCS and 75% of lebrikizumab 250 mg Q2W+TCS-treated participants maintained an IGA 0/1 response at 56 weeks of total treatment
- 81% lebrikizumab 250 mg Q4W+TCS and 86% of lebrikizumab 250 mg Q2W+TCS-treated participants maintained an EASI 75 response at 56 weeks of total treatment

Safety

In a pooled analysis on the placebo-controlled periods (weeks 0-16) of the 3 pivotal Phase 3 studies (ADvocate 1, ADvocate 2, ADhere) plus a Phase 2 dose-ranging study (Study J2T-DM-KGAF):

- Overall, the frequencies of treatment-emergent adverse events (AEs), serious adverse events (SAEs), and AEs leading to permanent discontinuation from study drug were similar in the lebrikizumab and placebo groups and were consistent between participants concomitantly treated with TCS and those receiving lebrikizumab as monotherapy. Most AEs were mild or moderate in severity.
- Conjunctivitis, herpes infection, and parasitic (Helminth) infection were defined as adverse events of special interest (AESIs) due to the potential association with the mechanism of action of lebrikizumab, the safety profiles of other drugs in the same class as lebrikizumab, and the heightened likelihood for these disorders in the AD population:
    - Conjunctivitis, including allergic, bacterial, and viral conjunctivitis, was reported more frequently in the lebrikizumab group (8.5%) compared to placebo (2.5%). Keratitis, also including related terms, was reported more frequently in the lebrikizumab group (0.6%) compared to placebo (0.3%). None of conjunctivitis or keratitis events were severe in intensity.

- Herpes zoster was reported more frequently in the lebrikizumab group (0.6%) compared to the placebo group (no events). None of herpes zoster events were severe in intensity.
- No events of parasitic infections were reported for the lebrikizumab or placebo groups in the pooled analysis of placebo-controlled periods. There was 1 parasitic infection reported in a participant in the ADhere study who was treated with lebrikizumab Q2W+TCS and continued treatment in ADjoin. This participant had a mild enterobiasis and ascariasis coinfection that was treated and the participant fully recovered. These events did not lead to treatment discontinuation.

- Increased blood eosinophil counts may be caused by IL-13 blockade leading to reduced chemotaxis and eosinophil trafficking from the blood to the airways or from the skin, resulting in eosinophil accumulation in the peripheral blood. Eosinophilia (defined as >5000 cells/mm^3) was uncommonly observed in participants treated with lebrikizumab (0.4%). In general, eosinophilia was transient and did not result in discontinuation. No eosinophilia-related disorders were reported.
- The frequency of injection site reactions (ISRs) was low overall and numerically higher in the lebrikizumab group (2.6%) compared to placebo (1.5%). The most frequently reported ISR symptoms in lebrikizumab-treated participants were injection site pain and erythema, none of which were severe in intensity.

During the maintenance period of the monotherapy studies (ADvocate 1 and ADvocate 2), participants treated with lebrikizumab 250 mg Q2W or Q4W reported similar frequencies of AEs and SAEs compared to placebo (lebrikizumab withdrawal).

5.2 Summary of the Known Potential Risks and Benefits

Patients with AD experience chronic relapsing disease characterised by skin lesions with intense itch and sleep disturbance that can significantly impair QoL (Bieber 2008, Silverberg 2018). The disease burden for patients with AD has been shown to have greater negative effects on mental health when compared to the disease burden caused by diabetes, hypertension (Zuberbier 2006), and psoriasis, another common and debilitating skin disease (Eckert 2018, Eckert 2019, Kiebert 2002, Langan 2020, Silverberg 2018, Vakharia 2017). The impact that depression, anxiety, and social dysfunction have on patients with AD also extends to their caregivers, and these negative impacts on QoL make AD the most burdensome skin disorder globally (Hay 2014, Zuberbier 2006).

Several therapies, including TCS, systemic corticosteroids, cyclosporine, JAK inhibitors, dupilumab, and tralokinumab are available to treat patients with AD. However, a substantial proportion of patients do not have adequate disease improvement, have loss of response to maintenance treatment, or fail to tolerate these treatments. Therefore, adults and adolescents with AD are still in need of alternative effective and safe treatment options.

Lebrikizumab treatment demonstrated key benefits by providing clinically meaningful improvement in patients with AD across a broad spectrum of disease outcomes including skin inflammation related to AD and itch. These improvements in disease severity, signs, and symptoms were seen rapidly after lebrikizumab treatment was initiated and equally well maintained up to 52 weeks by the administration of lebrikizumab 250 mg either Q2W or Q4W.

Overall, the majority of AEs during the pivotal Phase 3 studies were nonserious, mild or moderate in severity, and did not lead to treatment discontinuation. The key risk of

lebrikizumab that contributes most importantly to the benefit-risk evaluation for patients with AD is conjunctivitis. Conjunctivitis is an AESI in the current study and, if it occurs, will prompt additional data collection. As of now, clinical trial data in patients with moderate-to-severe AD indicate that lebrikizumab's risks do not outweigh the substantial clinical benefits observed in treated patients.

In conclusion, lebrikizumab has a positive benefit-risk profile and may help fulfil an unmet need for adults and adolescents with AD who have not been able to achieve disease improvements with or are intolerant of currently available treatment options.

5.3 Scientific Rationale for the Trial

Following the demonstration of efficacy and safety in the pivotal trials of lebrikizumab for the treatment of moderate-to-severe AD (see Section 5.1.5), this Phase 3b study seeks to evaluate clinical aspects of lebrikizumab treatment beyond those previously tested in the pivotal studies. Specifically, the study will examine the effectiveness and safety of lebrikizumab in a patient population with more moderate AD (see Section 7.2.2), the effectiveness and safety of lebrikizumab in patients previously treated with dupilumab (see Section 7.2.2), clinical responses to lebrikizumab Q4W dosing beginning at week 16 (see Section 7.2.3), and the impact of lebrikizumab treatment on AD in areas of the body that are difficult to treat (see Section 7.2.4). Furthermore, the study will provide insights into CCI [redacted] that may be affected by lebrikizumab treatment (see Section 10.7.2).

6 Objectives, Endpoints, and Estimands

6.1 Objectives and Endpoints

Table 2 outlines the objectives and corresponding endpoints that are to be assessed in the trial. All additional endpoints will be defined within the Statistical Analysis Plan (SAP).

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
To evaluate the effectiveness of 24 weeks of lebrikizumab in improving disease severity, signs, and symptoms in adults and adolescents with moderate-to-severe AD	**Primary Endpoint** • Percentage of participants achieving EASI score ≤7 at Week 24 **Secondary Endpoints** • Percentage of participants achieving EASI score ≤7, EASI ≤5, and EASI ≤3 by visit • Percentage of participants achieving EASI 75 and EASI 90 by visit • Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points by visit • Percentage of participants achieving SCORAD 75 and SCORAD 90 by visit • Percentage change from baseline in mTLSS (hands) from baseline by visit CCI [redacted]

Objectives	Endpoints
Secondary Objectives	
To evaluate the impact of 24 weeks of lebrikizumab treatment on patient-reported and Investigator-reported outcome measures in adults and adolescents with moderate-to-severe AD	**Secondary** *Pruritus* • Percentage of participants with Pruritus NRS ≥4 at baseline achieving ≥4-point improvement in Pruritus NRS from baseline by visit *Quality of Life* • Percentage of participants achieving DLQI 0-1 by visit • Percentage of participants with DLQI ≥4 at baseline achieving ≥4-point improvement in DLQI from baseline by visit • Percentage of participants achieving cDLQI 0-1 by visit • Percentage of participants with cDLQI ≥6 at baseline achieving ≥6-point improvement in cDLQI from baseline by visit *Sleep Loss Due to Itch* • Percentage of participants with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least 2-point reduction by visit *Disease Control* • Percentage of participants with POEM ≥4 at baseline achieving ≥4-point improvement in POEM from baseline by visit CCI [redacted]
Safety Objectives	
To evaluate the safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD	• Percentage of participants with treatment-emergent AEs including SAEs, related AEs, and AEs leading to study treatment discontinuation, and AESIs

CCI [redacted]

Abbreviations: AD=atopic dermatitis; AE=adverse event; AESI=adverse event of special interest; BSA=body surface area; cDLQI=Children's Dermatology Life Quality Index; DQLI= Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; EASI 75/90=75% or 90% reduction in EASI from baseline; mTLSS=modified Total Lesion Symptom Score; POEM=Patient Oriented Eczema Measure; Pruritus NRS=Pruritus Numerical Rating Scale; SAE=serious adverse event; SCORAD=Scoring Atopic Dermatitis; SCORAD 75/90=75% or 90% reduction in SCORAD from baseline; CCI [redacted]

6.2 Estimands

The clinical question of interest is: what is the proportion of patients who meet the clinical requirement for response AND without discontinuation due to lack of effectiveness, irrespective of use of prohibited medication for AD?

Therefore, the primary estimand of the primary and secondary objectives is described by the following attributes:

1. Population: Full Analysis Set (FAS) population as defined in Section 11.3.
2. Variable: apply to all primary and secondary effectiveness endpoints.
3. How to account for intercurrent events (ICE):
   a. Participants who discontinue treatment due to lack of effectiveness during the study will be considered as treatment failures, that is, non-responders, after the ICE. Therefore, a composite strategy (set to baseline) is used for these types of ICE. For participants who discontinue treatment due to any other reasons, a hypothetical strategy will be used to estimate what the treatment effect would have been if the participant had continued with treatment. Therefore, a hypothetical strategy (set to missing) is used for these ICE.
   b. Participants who are treated with a prohibited medication for AD during the study will not be considered as treatment failures after the ICE. Therefore, a treatment policy approach (observed) is used for these types of ICE.
4. Population-level summary: response proportions or means.

The supportive estimand of the primary and secondary objectives is described by the following attributes:

1. Population: Full Analysis Set (FAS) population as defined in Section 11.3.
2. Variable: apply to all primary and secondary endpoints.
3. How to account for intercurrent events (ICE):
   a. Participants who discontinue treatment due to lack of effectiveness during the study will be considered as treatment failures, that is, non-responders, after the ICE. Therefore, a composite strategy (set to baseline) is used for these types of ICE. For participants who discontinue treatment due to any other reasons, a hypothetical strategy will be used to estimate what the treatment effect would have been if the participant had continued with treatment. Therefore, a hypothetical strategy (set to missing) is used for these ICE.
   b. Participants who are treated with a prohibited medication for AD during the study will be considered as treatment failures after the ICE. Therefore, a composite strategy (set to baseline) is used for these types of ICE.
4. Population-level summary: response proportions or means.

For the estimand of the primary and secondary objectives, missing data including those as a result of ICE will be imputed based on Markov Chain Monte Carlo – multiple imputations (MCMC-MI) as described in Section 11.9.

7 Trial Design and Rationale

7.1 Trial Design

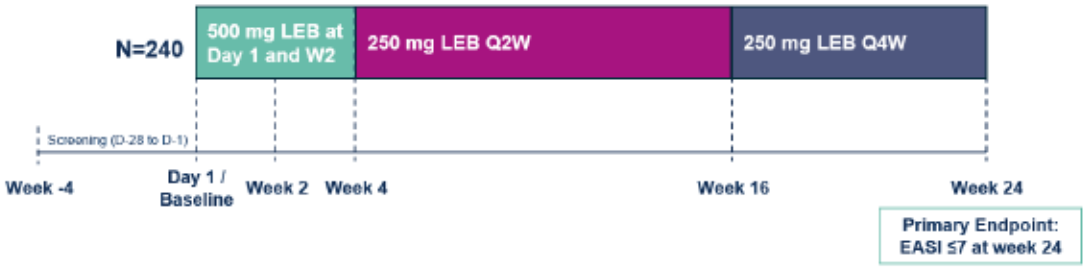
This is a single arm, open-label, Phase 3b study evaluating the effectiveness and safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD. The study will enrol approximately 240 participants.

Participants will be screened for study entry within 4 weeks of study Day 1. For eligible participants, loading doses of lebrikizumab 500 mg subcutaneous (SC) injection will be administered by site personnel at Day 1 and Week 2. Beginning at Week 4, lebrikizumab 250 mg will be administered Q2W, and participants will have the option of self-administration, following training of the participant and/or caregiver, or the participant may continue to receive injections at the study site. Beginning at Week 16, the dosing frequency will be reduced to every 4 weeks, and participants will receive lebrikizumab 250 mg SC injection Q4W up to Week 24.

Participants will undergo final study assessments at Week 24, ie, 4 weeks after the last dose of study medication at Week 20. For participants who withdraw from the study prior to Week 24, a safety follow-up visit will take place 4 weeks after the last dose of study medication.

The trial design is represented schematically in Figure 1.

Figure 1 Trial Design Schematic



Abbreviations: D=day; EASI=Eczema Area and Severity Index; LEB=lebrikizumab; Q2W=every other week; Q4W=every fourth week; W=week

7.2 Trial Rationale

7.2.1 Rationale for Trial Design

This is a single arm, open-label, Phase 3b study evaluating the effectiveness and safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD. A single-arm, open-label design is considered appropriate to achieve the objectives of the study, as the efficacy and safety of lebrikizumab were demonstrated the placebo-controlled pivotal study results (see Section 5.1.5.1).

7.2.2 Rationale for Trial Population

The severity of AD may be classified based on the EASI score, with scores of >7 to ≤21 indicating moderate disease and scores of >21 indicating severe to very severe disease (Hanifin 2022). In comparison with the pivotal trials, which recruited participants with an EASI score ≥16, the current study will allow enrolment of participants with more moderate disease (EASI ≥12); thus, contributing to product knowledge across a broader range of disease severity.

Dupilumab (Dupixent®) is an mAb that was authorised in the EU for the treatment of AD in 2017. Dupilumab binds IL-4Rα, inhibiting IL-4R signalling induced by both IL-4 and IL-13 (Harb 2020). This study will be enrolled such that up to 20% of all participants will have had prior exposure to dupilumab, including those with suboptimal responses. Data on the effectiveness and safety of lebrikizumab in patients previously treated with dupilumab are

limited. The results of a subpopulation analysis (N=20) from the ADhere study suggest that patients with prior dupilumab exposure can benefit from lebrikizumab treatment. However, additional data are needed to confirm this finding due to the small number of patients in the subpopulation (Gold 2023). Thus, this study will provide important information to clinicians on the effectiveness and safety of lebrikizumab in both naïve patients and patients previously treated with dupilumab.

7.2.3 Rationale for Trial Dose and Regimen

Atopic dermatitis is a heterogeneous disease in both its pathophysiology and clinical manifestation (Mastraftsi 2022), and the time under treatment to achieve clinical response is highly individual. In the pivotal trials (see Section 5.1.5.1), some participants with a partial clinical response at week 16 were observed to further improve with continued lebrikizumab Q2W treatment up to week 24. Results of this study will help to further characterise the clinical experience of adults and adolescents with moderate-to-severe AD who are treated with lebrikizumab Q4W beginning at Week 16, including participants with a partial response.

7.2.4 Rationale for Trial Assessments

The effectiveness assessments conducted in this study have been validated and extensively employed in patients with AD (Eichenfield 2014, Wollenberg 2018). Most of these assessments, EASI, IGA, Severity Scoring of Atopic Dermatitis (SCORAD), body surface area (BSA), were also employed in the pivotal trials of lebrikizumab. Patient-reported outcome measures that were assessed in the pivotal trials, Pruritus Numerical Rating Scale (Pruritus NRS), Dermatology Life Quality Index (DLQI)/Children's Dermatology Life Quality Index (cDLQI), Sleep-Loss Scale, and Patient Oriented Eczema Measure (POEM), are also included in this study for consistency in measures across studies.

In patients with AD, certain body areas are known to be more difficult to treat, including the hands, head, and neck, which can result in additional emotional burden and stigmatisation. In this study, the modified Total Lesion Symptom Score (mTLSS) will be assessed in participants with AD of the hands. The mTLSS is a validated tool to quantify the seven features of hand dermatitis (Gulliver 2018, Ruzicka 2008). CCI [redacted]

In addition to the Pruritus NRS, participants will complete the validated CCI [redacted] The CCI [redacted] is composed of a set of questions that describe several parameters related to pruritus (itch severity and duration, the need to scratch, and sleep disturbance due to itch) over the course of the day, and a score calculation enables a comparison of different time-points of assessment.

Participants will complete CCI [redacted], including the abbreviated CCI [redacted] and a CCI [redacted] will also be completed to capture the Investigator's considerations on the patient outcomes.

The timing of the effectiveness and patient-reported outcome (PRO) assessments reflects points when meaningful changes from baseline may be expected based on the experience in the pivotal trials, while minimizing the burden on the participants.

Safety assessments including AEs, safety laboratory test results (haematology, chemistry), concomitant medications, and physical examinations, which will be performed throughout the trial as shown in Table 1.

8 Selection of Trial Population and Withdrawal of Participants

8.1 Number of Participants

A sufficient number of patients with moderate-to-severe AD will be screened to enrol approximately 240 study participants, of which up to 20% will have had prior exposure to dupilumab.

Enrolment will be controlled to ensure representation from each of the participating countries (Germany, the United Kingdom, and the Netherlands).

For details on the sample size determination, refer to Section 11.1.

8.2 Inclusion Criteria

Participants eligible for inclusion in this trial must fulfil the following criteria:

1. Adults and adolescents (aged ≥12 to <18 years at the time of informed consent form (ICF)/informed assent form (IAF) signature and weighing ≥40 kg) who are candidates for systemic AD therapy.
2. Chronic AD (according to Hanifin and Rajka Criteria (Hanifin 1980)) that has been present for ≥1 year before the Screening visit.
3. EASI score ≥12 at the Day 1/Baseline Visit.
4. IGA score ≥3 (moderate) (scale of 0 [clear] to 4 [severe]) at the Baseline visit.
5. ≥10% BSA of AD involvement at the Day 1/Baseline visit.
6. History of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable.
7. Completed electronic diary (eDiary) entries for pruritus and sleep-loss for a minimum of 4 of 7 days before Day 1/Baseline.
8. Willing and able to comply with all clinic visits and study-related procedures and questionnaires.
9. For women of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or to use a highly effective contraceptive method during the treatment period and for at least 4 weeks or 1 menstrual period after the last dose of lebrikizumab.
    - NOTE: A woman of childbearing potential (WOCBP) is defined as a postmenarcheal woman, who has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause) and has not undergone surgical sterilisation (removal of ovaries and/or uterus).
    - NOTE: The following contraceptive methods are highly effective: combined (oestrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation, progestogen-only hormonal contraception (oral,

injectable, implantable) associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

10. Participant must provide signed ICF. Adolescent participants must also provide separate informed assent to enrol in the study and sign and date either a separate IAF or the ICF signed by the parent/legal guardian (as appropriate based on local regulations and requirements).

8.3 Exclusion Criteria

Participants fulfilling any of the following criteria are not eligible for inclusion in this trial:

1. Prior treatment at any time with tralokinumab, lebrikizumab, or an oral JAK inhibitor.
2. Intention to use any concomitant medication or therapy that is not permitted by this protocol or failure to undergo the required washout period for a particular prohibited medication (see Section 9.9.2).
3. History of anaphylaxis as defined by the Sampson criteria (Sampson 2006).
4. Uncontrolled chronic disease that might require bursts of oral corticosteroids, eg, co-morbid severe uncontrolled asthma (defined by an Asthma Control Questionnaire-5 score ≥1.5 or a history of ≥2 asthma exacerbations within the last 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalisation for >24 hours).
5. Occurrence of the following types of infection within 3 months before or during screening or development of these infections before Day 1 / Baseline:
   a. Serious (requiring hospitalisation, and/or IV or equivalent oral antibiotic treatment, as per the Investigator's opinion);
   b. Opportunistic (as defined by Winthrop et al. (Winthrop 2015))

      NOTE: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over;
   c. Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer);
   d. Recurring (including, but not limited to herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis).
6. Known current or chronic infection with any hepatitis virus.
7. Known liver cirrhosis and/or chronic hepatitis of any aetiology.
8. Known active endoparasitic infection or at high risk of these infections.
9. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgement.
10. History of human immunodeficiency virus (HIV) infection or known positive HIV serology.

11. Any clinically significant laboratory test results from the chemistry or haematology tests obtained at the Screening visit that would jeopardise the patient's participation in the study, per the Investigator's judgement.
12. Presence of skin comorbidities that may interfere with study assessments.
13. History of malignancy, including mycosis fungoides, within 5 years before the Screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin with no evidence of recurrence in the past 12 weeks.
14. Severe concomitant illness(es) that in the Investigator's judgement would adversely affect the participation in the study. Any other medical or psychological condition that in the opinion of the Investigator may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study participant because of his/her participation in this clinical trial, may make participation unreliable, or may interfere with study assessments.
15. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

8.4 Treatment Discontinuation and Trial Withdrawal Criteria

8.4.1 Trial Withdrawal Criteria

The Investigator will make reasonable efforts to keep each participant in the study. However, participants may withdraw or be withdrawn from the study for the following reasons:

- Voluntary withdrawal of consent to participate in the study participation, at any time (see Section 14.2)
- In the opinion of the Investigator, continued participation in the study is not in the best interest of the participant
- Important protocol deviation or procedure prohibited by the protocol
- Lost to follow-up

If at all possible, participants who withdraw from study will be requested to attend a Safety Follow-up (SFU) visit. The SFU visit should be performed 4 weeks after the last dose of study drug and may occur prior to the previously planned last study visit (Week 24, see Table 1). All information, including the reason for being withdrawn will be recorded in the participant's study records and in the electronic case report form (eCRF).

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Two attempts (eg, telephone contact, emails) to contact the participant must be documented in a participant's study records for all participants who are believed to be lost to follow-up. If it is determined that the participant has died, the site will use locally permissible methods to obtain the date and cause of death.

8.4.2 Treatment Discontinuation

Study drug must be permanently discontinued for participants who experience the following:

- Participant decision to stop treatment
- Severe non-compliance with study protocol, including use of a prohibited concomitant medication as outlined in Section 9.9.2.
- AEs, laboratory abnormality, or intercurrent illness for which continued treatment, that, in the opinion of the Investigator, would affect assessments of clinical status or participant safety to a significant degree
- Pregnancy
- Lack of effectiveness per the judgement of the Investigator

Participants who permanently discontinue study drug will be encouraged to continue study assessments up through Week 24. If the participant elects to withdraw from the study, an SFU visit will be performed 4 weeks after the last dose of lebrikizumab, as specified in Section 8.4.1.

All information, including the reason for permanent discontinuation of study drug will be recorded in the participant's study records and in the eCRF.

8.5 Screening Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the trial. A minimal set of screen failure information is required to be entered into the database to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from Competent Authorities. Minimal information includes demography, screen failure reason, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial (eg, screen failures) may be rescreened once. At the time of rescreening, the individual must sign a new ICF/IAF and repeat all Screening procedures.

8.5.1 Participant Replacement Criteria

An enrolled participant who withdraws from the trial at any time will not be replaced.

8.6 Termination of the Trial

8.6.1 End of Trial Definition

The "end of trial" is defined as the date when all participants enrolled in the trial complete Week 24 visit, or discontinue prior to this point, and this will be communicated to Competent Authorities and Independent Ethics Committee (IEC) in due time according to local regulations.

8.6.2 Completed Participant Definition

Participants attending the Week 24 visit will be considered "completed participants."

8.6.3 Premature Trial Termination

The Sponsor has the right to terminate the study at any time.

Certain circumstances may require the premature termination of the trial including:

- The Investigator/Coordinating Investigator and the Sponsor feel that the type, number, and/or severity of AEs justify discontinuation of the trial.
- New lebrikizumab efficacy or safety data emerges that would cause the benefit-risk profile (as specified in Section 5.2) to become negative for the treatment of adults and adolescents with moderate-to-severe AD.
- The Sponsor considers the applied doses of the trial drug to be no longer relevant.
- Data not known before becoming available and raise concern about the safety of the trial drug so that continuation would pose potential risks to the participant.

If the trial is terminated or suspended, the Sponsor will promptly inform the Investigators and the Competent Authorities. The IRB/IEC should be promptly informed and provided the reason(s) for the termination or suspension by the Investigator/ Sponsor, as specified by the applicable regulatory requirement(s).

The Investigator will inform the participants and will collect and keep all the data up to the date of discontinuation. Samples retrieved up to the date of trial termination will be analysed as per protocol.

If the trial is prematurely terminated or suspended, trial results will be reported according to the requirements outlined in this protocol as far as applicable.

The Clinical Data Interchange Standards Consortium criteria should be followed while recording the participant trial discontinuation reasons.

9 Treatments

9.1 Identity of Trial Investigational Medicinal Product(s)

Investigational medicinal product (IMP) manufacturing, labelling, packaging, and release will be done following Good Manufacturing Practice (GMP).

Test Investigational Medicinal Product

Substance Code/Name	Lebrikizumab
Route of Administration	Subcutaneous
Dosage Form	Solution for injection, containing 125 mg/mL lebrikizumab. Supplied as a sterile prefilled syringe (PFS) with a pre-assembled needle safety device
Unit Dose/Strength	Each PFS is intended for a single 2 mL dose (250 mg)
Packaging Description	White folding carton

Reference Investigational Medicinal Product

Not applicable

9.2 Packaging and Labelling

Packaging and labelling of IMP will be provided by the Sponsor and will comply with Annex VI of EU Clinical Trials Regulation 536/2014 and local regulatory requirements.

All study drugs will be labelled appropriately.

9.3 Shipment, Storage, and Accountability

Only participants enrolled in the trial may receive trial IMP and only authorized site staff may supply or administer trial IMP. All drug supplies must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, pharmacist, or designee will confirm receipt of the study drug, will verify the condition under which the drug was received, and will verify the contents of the shipment immediately upon receipt of the product.

The Investigator, the trial staff, institution, or the head of the medical institution (where applicable) is responsible for clinical supplies accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), following Sponsor's instructions. The Investigator and trial staff must adhere to Good Clinical Practice (GCP) guidelines, as well as local or regional requirements. Under no circumstances will the Investigator allow the trial drugs to be used other than as directed by this protocol. Clinical supplies will be dispensed only by an appropriately qualified person and will not be dispensed to any individual who is not enrolled in the trial.

Participants will be instructed to return the used medication to the study site at the next study visit. Used medication can be thrown away into special containers for injectable and medical waste, and empty boxes must be stored for final accountability. Unused medication will be returned to the Sponsor or designee, where the remaining medication will be destroyed according to standard operating procedures (SOPs). Sites may destroy unused medication as long as, before destruction, it has been verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials. Retention drug samples will be kept by the Sponsor during the trial and until it is legally required after trial completion.

Further guidance and information for the final disposition of unused trial interventions are provided in the Investigator's Drug Manual and/or Pharmacy Manual.

9.4 Treatment Administration

Treatment will begin on Day 1, after confirmation of participant eligibility and collection of all predose samples and assessments.

Loading doses of lebrikizumab 500 mg subcutaneous (SC) injection will be administered by site personnel at Day 1 and Week 2. Beginning at Week 4, lebrikizumab 250 mg will be administered Q2W, and participants will have the option of self-administration, following training of the participant and/or caregiver, or the participant may continue to receive injections at the study site. Beginning at Week 16, the dosing frequency will be reduced to every 4 weeks, and participants will receive lebrikizumab 250 mg SC injection Q4W up to Week 24 (ie, last Q4W dose administered at Week 20).

9.5 Treatment Compliance

Study drug compliance will be assessed by counting returned used or unused prefilled syringes. A participant will be considered compliant with the dosing regimen if the participant received ≥75% of the expected number of injections while enrolled in the study. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

The dosing logs for each participant will be kept during the trial. The Clinical Research Associate (CRA)/Monitor will review treatment compliance during monitoring site visits.

9.6 Methods for Assigning Participants to Treatment Groups

9.6.1 Participant Identification

To protect the participant's identity and data confidentiality, each participant will be identified in the trial with 1 unique participant unique identifier. This number will be associated with the participant throughout the study. Every participant who signs an ICF/IAF must be assigned a participant number. This 11-digit number will consist of a 3-digit country-specific code, followed by a 5-digit site identification, and a 3-digit number assigned sequentially within each site to each participant, starting at 001.

The site number will be predetermined, but the sequential participant number is determined when entering the participant in electronic data capture (EDC). The site staff must enter the participant details in EDC upon signing the ICF/IAF. At each site, the first participant is assigned participant number 001, and subsequent participants are assigned consecutive numbers.

Once assigned to a participant, the participant number will not be reused. The participant number will be used to identify the participant throughout the trial.

9.6.2 Randomization

Not applicable. There is no control arm in this study; all participants are treated with IMP.

9.7 Blinding

Not applicable. This is an open-label study.

9.8 Unblinding by the Investigator

Not applicable.

9.9 Concomitant and Post-trial Medications/Therapy

9.9.1 Concomitant Medications

Any medication taken for medical reasons (mainly diseases concomitant with studied disease) before trial entry, will be continued at the same dose and under the same conditions, at the discretion of the Investigator. All chronic medications will be recorded.

At the Day 1/Baseline visit all participants will be asked to provide information about concomitant medications taken 4 weeks prior to the Day 1/Baseline visit, as well as any prohibited medications within the prior 6 months (see Table 3). Participants should be instructed to consult with the Investigator prior to initiating any new medication (either self-administered non-prescription drugs or prescription therapy prescribed by another physician) while participating in the study. For participants previously treated with dupilumab, the reason for discontinuation will be captured in the eCRF.

Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem. If the need for concomitant medication arises, the Investigator should base decisions on the participant and clinical factors. Any additional medication (including the limited use of therapeutic agents which, if used under treatment regimens other than for treatment an AE or for appropriate medical management, might be considered therapies), whether prescription or non-prescription, used at baseline and/or during the course of the study, must be documented, including the dose and regimen, start and stop dates, and indication.

Permitted concomitant medications during the study include:

- Non-medicated moisturizers are to be used during the study. Participants may continue to use her/his current over-the-counter moisturizer regimen, if approved by the Investigator.
- Lebrikizumab monotherapy is recommended, but the concomitant use of low and mid-potency TCS is permitted, per the Investigator's discretion, for participants on a stable regimen at baseline. The baseline TCS regimen and any changes during the study will be captured in the eCRF.
- Intermittent use of other topical medications (ie, TCIs and PDE4 inhibitors) is permitted for the treatment of worsening AD symptoms during the trial.
- Acute infections can be treated with systemic antibiotics.

Short-term treatment (≤30 days) with high-potency TCS or systemic corticosteroid treatment for symptoms of AD is permitted, but extended use (>30 days) of high-potency TCS or systemic corticosteroids for the treatment of AD is prohibited.

9.9.2 Prohibited Concomitant Medications

Both prior and concomitant use of tralokinumab and oral JAK inhibitors is prohibited. Prior use of dupilumab is allowed, following an 8-week washout prior to Day 1/Baseline, but concomitant use of dupilumab is prohibited. The concomitant use of systemic corticosteroids for the treatment of AD is prohibited, except as specified in Section 9.9.1. Chronic treatment with systemic antibiotics for infections is not permitted.

Other drugs that are prohibited during the trial are listed in Table 3, but prior use is permissible after expiration of the washout period.

Table 3 Prohibited Concomitant Medications and Washout Period for Prior Use

Prohibited Medications	Washout Period Prior to Baseline
High-potency TCS except for short-term use as specified in Section 9.9.1 Topical calcineurin inhibitors and phosphodiesterase-4 inhibitors, such as crisaborole, except for intermittent use as specified in Section 9.9.1; cannabinoid treatment for AD	2 weeks
• Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids (>30 days), cyclosporine, mycophenolate-mofetil, interferon-γ, azathioprine, methotrexate, etc.) • Phototherapy and photochemotherapy for AD • Regular use (more than 2 visits per week) of a tanning booth/parlour	4 weeks
An investigational drug	8 weeks or 5 half-lives (if known), whichever is longer
Dupilumab	8 weeks
Live (attenuated) vaccine	12 weeks
Other biologics	16 weeks or 5 half-lives (if known), whichever is longer
B cell-depleting biologics, including but not limited to rituximab	6 months

Abbreviations: AD=atopic dermatitis; TCS=topical corticosteroid

9.9.3 Post-trial Medications

Once the last IMP dose is taken (last visit where the participant takes IMP), and related trial measurements are completed, participants should continue to take their usual medications, those allowed during the trial as well as other medications interrupted prior to trial enrolment, as deemed appropriate by the Investigator.

It is not planned to treat participants with lebrikizumab any further than scheduled in this trial. The trial drug is for experimental use only and there are other therapies available to treat the disease.

10 Trial Procedures and Assessments

10.1 General Conditions of the Trial

Informed consent must be obtained before performing any procedure related to the trial. The ICF/IAF must be signed after the participant has received sufficient information about the trial and after he/she has had the opportunity to ask any questions and consider other treatment options. Participation in the trial must be documented in the participant's medical records and a copy of the ICF/IAF will be given to the participant.

At the scheduled protocol visits, IMP dosing must occur while being witnessed by the research personnel at the clinic to ensure the proper IMP application, as well as the correct timing of activities to occur before and after dosing.

Trial visit dates must be scheduled with respect to Day 1/Baseline visit. To adapt appointments to local holidays, participant's availability, or site internal organisation needs, visit time windows are allowed as specified in Table 1. Patient-reported outcome questionnaires must be completed prior to other study-related activities. Therefore, the visit window for patient-reported outcomes is -3 days for Week 2, then -5 days through Week 16, and -7 days for Week 24. Please contact the CRA or CRO Medical Monitor for advice in case of exceptional situations.

The study drug should be administered after all other procedures and assessments have been completed at applicable visits.

PROs will be assessed prior to or at the start of the visit (see Table 1) before any other assessments or procedures. It is recommended that assessments or procedures be performed in the following order: 1) patient-reported outcomes; 2) Investigator assessments and other effectiveness assessments, 3) safety and laboratory assessments, 4) blood sampling for genomics and CCI and 5) administration of study drug.

Laboratory tests will be performed using the equipment provided by the Sponsor for trial purposes through a specialised provider, who will perform centralised assessment and reporting.

Optimally, the evaluations for each participant (review of treatment compliance, etc.) should be performed by the same Investigator throughout the trial to avoid inter-assessor bias. In addition, applicable questionnaires and assessments administration will be performed by an assessor who is trained and certified by the Sponsor or delegate as appropriate.

10.2 Participants General Conditions During the Trial

After the Screening evaluation and while not at the research site, participants will maintain normal daily activities, following the instructions of the Investigator. Participants will be asked to adhere as much as possible to the following general requirements:

- Do not donate blood from the Screening Visit to 1 month after the last study visit.
- No use of hard drugs or other prohibited substances.
- Contraception, if assigned, is used consistently and correctly as outlined in Section 8.2.
- Female participants will inform the study staff of any changes in childbearing potential.
- On the days of study visits, topical therapy should not be applied before the participant has undergone all study procedures and clinical evaluations including adequate assessment of skin dryness.

Any event likely to interfere with the objectives of the trial will be communicated to the Investigator and reported without delay to the Sponsor.

10.2.1 Instructions for Male Participants

Male participants are not required to use any contraception except in compliance with specific local government study requirements.

10.3 Scheduled Activities and Trial Visits

10.3.1 Screening Period

The ICF must be signed before any trial-related procedures are performed (see Section 14.2). The Screening Period will start with the Screening Visit and continue up to Day 1/Baseline.

Before signature of the ICF/IAF, Investigators will evaluate eligibility of participants for entry in the trial by comparing past and current medical status, as documented in the participant's medical records, to the trial's inclusion/exclusion criteria.

Eligible participants will receive a detailed description of all activities and requirements before signing the ICF/IAF to ensure their understanding and compliance with sample collection, clinical examination, and eDiary completion requirements.

Participants who require a washout period from prohibited concomitant treatments should be seen and sign the ICF/IAF before the Screening visit to ensure the necessary washout period is met as required based on the type of background therapy taken (see Section 9.9.2). No trial assessments will be performed on that date and the Screening visit will be scheduled according to the washout length required for the specific medication stopped.

The screening visit and assessments will be performed in accordance with schedule detailed in Table 1.

Data on demographic and baseline characteristics will be collected during screening. Skin type will be recorded according to the Fitzpatrick scale (Fitzpatrick 1988).

10.3.2 Treatment Period

Enrolment begins at Day 1/Baseline for eligible participants. Treatment period visits and assessments will be performed in accordance with the schedule detailed in Table 1. See Sections 10.4 and 10.5 for details on the effectiveness and safety assessments, respectively.

The trial visits cannot be repeated or skipped but may be postponed (if not started yet) within the time windows allowed on this protocol, in case of:

- technical problems with the equipment necessary for the visit,
- any AEs that impede conduct of the visit, or
- the intake of any prohibited medication, to reach the washout length required on the specific prohibited medication section of the protocol, as long as the delay fits the protocol allowed time window. If the delay is longer than the protocol allowed time window, the visit will take place but only the safety assessments (assessment of AEs, etc.) will be performed.

After starting any visit procedure but before the IMP administration, any treatment visit can be rescheduled to be performed on another day.

After IMP administration, re-scheduling of visits is not allowed.

10.3.3 Follow-up Period

Participants will undergo final study assessments at Week 24, ie, 4 weeks after the last dose of study medication at Week 20. For participants who withdraw from the study prior to Week 24, a safety follow-up visit will take place 4 weeks after the last dose of study medication.

10.3.4 Unscheduled and Repeated Tests

Unscheduled Tests

As deemed necessary by the Investigator, additional safety test(s) can be performed at any time during the trial in order to follow-up the progress of any clinically relevant abnormal finding, investigate any potential new adverse event, etc. These additional tests outside of the initial schedule of the trial will be considered "unscheduled tests" and will not be associated with any trial visit.

Repeated Tests

Any safety test may be repeated at the Investigator's discretion under either of the following situations:

- When there is any kind of problem with the first test (ie, blood sample haemolysed, presence of artefacts, etc.). The Investigator should repeat the individual test as soon as possible.
- At the Screening visit any individual test(s) may be reasonably repeated prior to Day 1/Baseline to confirm the eligibility criteria (eg, laboratory sample when there is any clinically significant abnormality, etc.).

The new test will be considered a "re-test" and will be identified with the same visit ID as the first attempt.

10.4 Effectiveness Assessments

Each participant's AD will be assessed as specified in Table 1. Whenever possible, the same assessor should perform all assessments on a given participant during the course of the study. The Sponsor or delegate will administer training on the required effectiveness assessments, and details on the specific instruments and training given will be recorded in the study training materials. If a parent or caregiver helps an adolescent participant complete an assessment or questionnaire, they must not influence or question the response given by the adolescent participant with AD. This requirement should be communicated to the parent or caregiver during training on eDiary completion.

10.4.1 Eczema Area and Severity Index Score

The EASI is used to assess the severity and extent of AD; it is a composite index with scores ranging from 0 to 72, with higher values indicating more severe and or extensive disease (Hanifin 2001). The severity of erythema, induration/papulation, excoriation, and lichenification will be assessed by the Investigator or trained designee on a scale of 0 (absent) to 3 (severe) for each of the 4 body areas: head/neck, trunk, upper limbs, and lower limbs, with half points allowed. In addition, the extent of AD involvement in each of the 4 body areas will

be assessed as a percentage by body area of head/neck, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. Assessors must be trained and certified by the Sponsor or delegate before conducting this assessment.

10.4.2 Investigator Global Assessment

The IGA is an instrument used to globally rate the severity of a patient's AD. It is based on a 5-point scale ranging from 0 (clear) to 4 (severe) (Table 4), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point. Assessors must be trained and certified by the Sponsor or delegate before conducting this assessment.

Table 4 Investigator Global Assessment

Score	Grade	Definition
0	Clear	Minor, residual discolouration; no erythema or induration/papulation; no oozing/crusting; no oedema.
1	Almost clear	Trace, faint-pink erythema with barely perceptible induration/papulation and no oozing/crusting; no oedema.
2	Mild	Faint-pink erythema with papulation and oedema perceptible upon palpation and no oozing/crusting; minimal induration.
3	Moderate	Pink-red erythema with definite oedema of skin papules and plaques; there may be some oozing/crusting; palpable induration.
4	Severe	Deep/bright red erythema with significant swelling and obvious raised borders of papules and plaques with oozing/crusting; significant induration.

10.4.3 Body Surface Area

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. Body surface area will be determined by the Investigator or designee using the patient palm=1% BSA rule. Assessors must be trained and certified by the Sponsor or delegate before conducting this assessment.

10.4.4 Scoring Atopic Dermatitis

The SCORAD is a validated clinical tool for assessing the extent and intensity of AD (ETFAD 1993). There are 3 components to the assessment:

- The AD surface involvement is assessed as the proportion of involved surface area segment by segment by applying the rule of 9s (eg, 50% of the right leg = 4.5) and reported as the sum of all areas, with a score ranging from 0 to 100.
- The intensity part of the SCORAD consists of 6 items: erythema, oedema, oozing/crusting, excoriation, lichenification, and dryness. Each item is graded as follows: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points).
- Subjective assessment of itch and of sleeplessness is recorded for each symptom using a visual analog scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), for a maximum possible score of 20.

The SCORAD Index formula is: A/5 + 7B/2 + C. In this formula "A" is defined as the extent (0-100), "B" is defined as the intensity (0-18), and "C" is defined as the subjective symptoms (0-20). The maximum score of the SCORAD Index is 103.

Assessments will be reported by the clinician and the participant (visual analogue scale only). Assessors must be trained and certified by the Sponsor or delegate before conducting this assessment.

10.4.5 Pruritus Numerical Rating Scale

The Pruritus NRS is an 11-point scale used by patients to rate their worst itch severity over the past 24 hours, with 0 indicating "No itch," and 10 indicating "Worst itch imaginable" (Phan 2012). Assessments will be recorded by the participant using an eDiary.

The baseline Pruritus NRS will be determined based on the average of daily Pruritus NRS scores during the 7 days immediately before the Day 1/Baseline visit. A minimum of 4 daily scores out of the 7 days immediately before Day 1/Baseline visit is required for this calculation.

10.4.6 Sleep-Loss Scale

Sleep loss will be assessed by all participants using a PRO instrument. Participants (and if applicable, with help of parents/caregiver if required) will rate their sleep loss on a 5-point Likert scale (with scores ranging from 0 [not at all] to 4 [unable to sleep at all]). Assessments will be recorded by the participant using an eDiary.

The baseline Sleep-Loss Scale score will be determined based on the average of daily Sleep-Loss Scale scores during the 7 days immediately before the Day 1/Baseline visit. A minimum of 4 daily scores out of the 7 days immediately before Day 1/Baseline is required for this calculation.

10.4.7 Patient-Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire completed by the participant (and, if applicable, with help of parents/caregiver if required) to assess disease symptoms (Charman 2004). Patients are asked to respond to questions on skin dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping. All answers carry equal weight, with a total possible score ranging from 0 to 28 (answers scored as: No days=0; 1 to 2 days=1; 3 to 4 days=2; 5 to 6 days=3; every day=4). A high score is indicative of a poor QoL. POEM responses will be captured using an eDiary.

10.4.8 Dermatology Life Quality Index

The DLQI is a 10-item validated questionnaire completed by the participant or caregiver used to assess the impact of skin disease on the participant's QoL during the previous week (Finlay 1994). The 10 questions cover the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, and treatment. Each question is scored from 0 to 3 ("not at all," "a little," "a lot," and "very much"), giving a total score ranging from 0 to 30. A high score is indicative of a poor QoL.

Adolescents younger than age of 16 years will use the CDLQI, which is based on a set of 10 questions different from those of the DLQI (Finlay 1994).

10.4.9 Modified Total Lesion Symptom Score

The mTLSS is a validated tool to quantify (0=none, 1=mild, 2=moderate, and 3=severe) the seven features of AD of the hand (erythema, scaling, lichenification/hyperkeratosis, vesiculation, oedema, fissures, pruritus/pain) for a maximum score of 21 (Ruzicka 2008). The most affected side (palmar or dorsal) of the hand most severely affected will be assessed and scored.

CCI

[redacted]

CCI

[redacted]

10.5 Safety and Tolerability Assessments

10.5.1 Adverse Events

See Section 10.6 for adverse event definitions and reporting requirements.

10.5.2 Medical History

A detailed medical history of current medical conditions, including other atopic disorders, will be obtained by the Investigator or qualified designee at the Screening visit and recorded in the eCRF.

Participant history should include information on clinically significant personal history including identification of major cardiovascular risk factors, current and past smoking history, current alcohol use, past history of infections, malignancies, and major cardiovascular conditions.

Information on the participant's AD and comorbidities (past history of asthma, allergic rhinitis, food allergies, alopecia, eye disorders) will be collected and include the date of onset, extent of involvement and past treatments for AD and comorbidities, and any family history.

For participants previously treated with dupilumab, the reason for having discontinued dupilumab will be captured in the eCRF.

10.5.3 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded to allow calculation of body mass index (BMI). For this, participants should be in light indoor clothes without shoes.

The presence of AD specifically on the CCI and hands will be documented in the eCRF.

10.5.4 Laboratory Testing

Routine laboratory assessments will be performed at a designated central laboratory. Tests to be performed are detailed in Table 5.

Table 5 Laboratory Testing Parameters

Assessment	Specific Tests
Haematology	Haematocrit, haemoglobin, erythrocytes (red blood cells count), mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, leucocytes (white blood cells count), differential blood count (absolute and % of neutrophils, lymphocytes, monocytes, eosinophils and basophils), thrombocytes (platelet count)
Blood chemistry	Electrolytes: Sodium, potassium, chloride, calcium, inorganic phosphate Enzymes: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, lactate dehydrogenase, and creatine-kinase Substrates: Glucose, total cholesterol, triglycerides, urea, creatinine, total bilirubin, total protein, albumin, uric acid, and blood urea nitrogen
Pregnancy Testing	A serum β-hCG test will be performed in all pre-menopausal women. All pre-menopausal women who are not sterile at screening will also have a urine pregnancy test performed locally according to the schedule in Table 1. Any woman with a confirmed positive pregnancy test during screening is not eligible for study participation.

Assessment	Specific Tests
	A positive urine pregnancy test during the treatment period of the trial requires a serum β-hCG test in order to confirm the result.

Abbreviations: β-hCG=beta-human chorionic gonadotropin

Blood samples for laboratory testing will be collected in appropriate sampling tubes according to the Schedule of Assessments (Table 1).

All abnormal laboratory test results will be evaluated by the Investigator, and the evaluation of clinically significant abnormalities will be specifically documented.

10.6 Adverse Events

The Investigator will closely monitor any AE and will adopt the necessary clinical measures to ensure the safety of the participant.

10.6.1 Definitions

Adverse Event

An AE is defined as any untoward medical occurrence in a clinical trial participant, regardless of the administration of the IMP and its causal relationship to it.

An AE can therefore be any unfavourable and unintended medical occurrence during the patient's participation in the trial, including deterioration of a pre-existing medical condition, an abnormal value in a laboratory assessment, ECG abnormality, or an abnormal finding in the physical examination.

AEs must be temporally associated with the patient's participation in the trial, ie, occur after signing the ICF. At the time of the occurrence of an AE, the administration of the IMP does not need to have been initiated yet. If initiated, it does not necessarily need to have a positive causal relationship to the event.

Adverse Event of Special Interest

The following treatment-emergent AEs are being designated as AESIs:

- conjunctivitis
- herpes simplex or zoster infection
- parasitic (helminthic) infections

Additional data will be collected for AESIs and a specific follow-up form for conjunctivitis will be provided to the site. Participant records will include any follow-up information regarding these AESIs.

Serious Adverse Event

An SAE is an adverse event, which falls into one or more of the following categories:

- results in death,

- is life-threatening (ie, an event which, in the view of the Investigator, places the participant at immediate risk of death from the event as it occurred.) It does not mean that the event might hypothetically have caused death if it was more severe or lasted longer,
- requires inpatient hospitalisation or prolongs existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect, or
- is any other medically important event that may jeopardise the participant or may require intervention to prevent one of the other above outcomes.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or do not result in death or hospitalisation but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. These are considered "other important medical events."

Inpatient hospitalisation means that the participant has been admitted to the hospital for inpatient care, either to the inpatient ward or to the emergency room for observation and/or treatment that could not have been appropriate in the physician's office or outpatient setting.

Prolongation of hospitalisation is defined as any extension of an inpatient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician.

The following events do not meet the criteria for seriousness:

- Hospitalisation for a treatment/surgical procedure which was elective or pre-planned for a pre-existing condition that did not worsen during the participation in the trial does not meet the criteria for seriousness.

10.6.2 Reporting of Adverse Events

Adverse events either reported by the participant or observed by the Investigator must be recorded on the AE page of the eCRF and should be described in the following manner:

- The nature of the AE will be described in precise, standard medical terminology (ie, not necessarily the exact words used by the participant). If known, a specific diagnosis should be recorded instead of listing signs and symptoms (eg, allergic contact dermatitis).
- The duration of the AE will be described by the start date and end date.
- The location for cutaneous adverse events will be described as at or just around the application area (≤2 cm from the application area) or distant (>2 cm from the application area).
- The intensity of the AE will be described according to the Investigator's clinical judgement, and assigned to one of the following categories:
  - **Mild**: Awareness of event, symptoms or signs, but easily tolerated (acceptable).
  - **Moderate**: Sufficient discomfort and interferes with usual activity (disturbing).

- **Severe**: Incapacitating with inability to do normal daily living activities or significantly affects clinical status and warrants intervention (unacceptable).

- The causal relationship of the event to use of the IMP will be described in terms of:
  - **Not related**: Event or laboratory test abnormality, definitely not related to trial drug, as related to other drug, chemicals or underlying disease.
  - **Unlikely related**: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable; disease or other drugs, chemicals or underlying disease provide plausible explanations.
  - **Possibly related**: Event or laboratory test abnormality, with a reasonable time relationship to drug intake; could also be explained by underlying disease or other drugs or chemicals; information on drug withdrawal may be lacking or unclear.
  - **Related**: Event or laboratory test abnormality, with a reasonable time relationship to drug intake, unlikely to be attributed to underlying disease or other drugs or chemicals; response to withdrawal clinically reasonable (positive dechallenge).

  Possibly related and related terms will be considered "related" terms for reporting purposes. If the events are assessed as unlikely related or not related to the suspect IMP, the event does not qualify for reporting purposes. In the absence of information on causality from the reporting Investigator, the CRO will immediately contact the reporting Investigator to request a causality assessment. The case will be updated with the follow-up information and reported accordingly. If no causality is provided by the Investigator, the Sponsor assessment will be considered for submission purposes.

- The outcome of the event will be described in terms of:
  - Recovered/resolved
  - Recovering/resolving
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal
  - Unknown

- The action taken on the IMP will be captured as:
  - Drug withdrawn
  - Dose interrupted
  - Dose not changed
  - Not applicable

AEs will be collected only once with its maximum severity, except when the AE started before first IMP administration, persisted after it and worsened in severity any time after first IMP. In this latter case, the AE will be collected with each respective severity. AE term recorded must be exactly the same in the different timepoints where AE is reported in the eCRF.

10.6.3 Recording of Adverse Events

Adverse events will be recorded in the eCRF from signature of the ICF up to the Week 24 visit, or the safety follow-up visit 4 weeks after last trial drug administration for participants who withdraw from the study.

Medical disorders present at the time of signing the informed consent that are part of the participant's medical history will only be considered AEs if they worsen after this time.

Abnormalities detected before IMP administration in physical exam, laboratory tests, ECGs, or other safety assessments will not be considered AEs if already known as part of the medical history or in relation to prior medical conditions and will be recorded on the eCRF/CRF Medical History/physical examination form/page. However, abnormalities detected in screening/baseline tests, thought to be due to a trial procedure, will be considered AEs.

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligations to report as AEs.

Abnormalities (newly occurring or worsening of previously known abnormalities) detected after IMP administration in physical exam, laboratory tests, or other safety assessments, which are considered clinically significant by the Investigator or which require an intervention or a diagnosis test, or may result in the IMP discontinuation, should be reported as AEs.

Reported terms should accurately characterise the adverse event. When a participant experiences unspecified injury, signs and symptoms, active investigation should be conducted to reach final diagnosis. Disease diagnosis would be the preferred reported term.

AEs will be elicited by asking the participants non-leading questions (eg, "How do/did you feel?") and by collecting AEs spontaneously reported by the participant to the Investigator or a designee.

All AEs elicited by the Investigator during the defined AE collection period must be recorded on the eCRF. In addition, when an AE meets the criteria of seriousness (ie, an SAE), it must also be recorded on the SAE form and reported following the defined timelines in Section 10.6.4.

10.6.4 Reporting of Serious Adverse Events

Serious adverse events will be recorded in the eCRF from signature of the ICF up to the Week 24 visit, or the safety follow-up visit 4 weeks after last trial drug administration for participants who withdraw from the study.

The Investigator must report any SAE within 24 hours from the moment she/he first learns of it to the Sponsor/CRO pharmacovigilance unit on a SAE report form. This reporting will take place regardless of whether the Investigator considers the event to be causally related to the IMP(s), to any other medicinal product(s), to the clinical trial procedure or to any intervention undergone by the participant.

Original reports are to be kept by the Investigator in the Investigator's File.

The trial centre must transmit the SAE report form and/or pregnancy form to the CRO pharmacovigilance unit. Contact details and specific instructions on the flow of the SAE will be provided to all sites by the CRO.

The minimum information that must be included in the initial report is:

- An event meeting the criteria of SAE,
- A qualifiable reporter, defined as an Investigator of this trial or his/her delegate,
- A qualified participant, defined as a patient who has consented to this trial,
- A suspect medicinal product, and
- The Investigator's causality assessment.

Unless the SAE has been sufficiently documented in the initial report, the Investigator will provide all available additional information in follow-up reports by using a new form and adhering to the same routing and time frames as defined for the initial report. This will be continued until the event has been fully documented and reported.

An event reported to the Sponsor/CRO pharmacovigilance unit which does not meet the SAE criteria shall be nullified by the Investigator by forwarding a follow-up report.

A regulatory report of the SAE (depending on the local requirements) will be produced by the Sponsor/CRO pharmacovigilance unit and submitted to the Competent Authorities, IEC and/or Investigators, when applicable according to local regulations.

10.6.5 Suspected Unexpected Serious Adverse Reactions

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (ie, the event is not consistent with the reference safety information, as reflected in Section 4.8 of the SmPC)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The Investigator will assess whether an event is causally related to study treatment. The Sponsor (or designee) will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC (where required) within 7 days after the Sponsor (or designee) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IECs within 15 calendar days after the Sponsor (or designee) first has knowledge of them.

The Sponsor (or designee) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities (including reporting to the Eudravigilance database) and for informing Investigators of reportable events, in compliance

with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IECs of reportable events within the applicable timeframes.

10.6.6 Follow-up of Adverse events / Serious Adverse Events

Those AEs/SAEs recorded for the Screening Failure patients will be followed-up until resolution or until otherwise agreed between the Sponsor and the Investigator.

All AEs/SAEs that are still present after the last trial drug administration (including AEs that have led to premature discontinuation), will be followed-up at least 4 weeks, unless otherwise specified in the protocol after the last trial drug administration, by means of a follow-up contact or visit (whichever is considered more appropriate by the Investigator). In case the AE/SAE is still ongoing after that timepoint, this will be followed-up until its resolution or until otherwise agreed between the Sponsor and the Investigator. The same timeframes will apply for AEs from screening failures which are ongoing at the time the participant is withdrawn from the trial.

Additional safety data collected after the follow-up contact/visit to follow-up the ongoing AE will not be included into the clinical database, if this was already locked; therefore, the clinical database lock will not be delayed due to this situation. Any SAE will be followed up if needed after clinical database lock and the information will be only stored in the safety database.

10.6.7 Overdose

An overdose is defined as any dose higher than the maximum dose described in the study protocol.

If an overdose leads to an AE, the AE will be recorded in the eCRF. In addition, if the overdose leads to an AE meeting the criteria of seriousness (ie, an SAE), the SAE form will be completed with all the available information and reported within the same timeframe and following the same routing as for a SAE (see Section 10.6.4). The participant must be followed-up and the Investigator will make every effort to obtain information on how the overdose was managed, any treatment administered and the final outcome. This follow-up information will be reported, following the same procedure and timeframes as for the initial report.

10.6.8 Pregnancies

Investigators must instruct female participants to inform them immediately if they become pregnant during the trial and up to 30 days or 1 menstrual period after last IMP dose, whichever is longer.

In case of pregnancy during the participation in the trial, the participant will be immediately considered for discontinuation from the study.

All pregnancies beginning during the participant's participation in the trial or up to 30 days or 1 menstrual period after last IMP administration, whichever is longer, which come to the knowledge of the Investigator, after the clinical trial termination will be reported to the Sponsor/CRO pharmacovigilance unit as throughout the trial.

The Sponsor will be informed according to the safety reporting procedure: the Investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it

to the CRO pharmacovigilance unit within 24 hours of confirmation of the pregnancy. Pregnancy is not itself an AE or SAE; however, maternal/foetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate.

The Investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, the follow-up period will be deemed to have ended when the health status of the child has been determined on its birth or after an appropriate period post-delivery considered necessary to monitor the development of the newborn is completed.

The subject will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriage, developmental delay, foetal death, SAE in a neonate and congenital abnormalities will be reported as SAEs. The Investigator will inform the CRO pharmacovigilance unit of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the Sponsor and, when applicable, to the ethics committee.

All pregnancies in the female partners of male subjects receiving at least one administration of the study drug will be recorded from first dose to 12 weeks after last IMP dose. Investigators must instruct male subjects to inform them immediately if their female partner becomes pregnant during the trial and up to 12 weeks after last IMP dose.

10.6.9 Unblinding for Safety Reasons

Not applicable.

10.6.10 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention. The Sponsor collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements. Participants will be instructed to contact the Investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

Time Period for Detecting Product Complaints:

- Product complaints that result in an AE will be detected, documented, and reported to the Sponsor during all periods of the study in which the drug is used.
- If the Investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the Investigator will promptly notify the Sponsor.

Prompt Reporting of Product Complaints to Sponsor:

- Product complaints will be reported to the Sponsor within 24 hours after the Investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the Sponsor.

Follow-up of Product Complaints:

- Follow-up applies to all participants, including those who discontinue study intervention.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator and submitted to the Sponsor.

10.7 Other Assessments

10.7.1 Genomics

A blood sample for DNA isolation (genomics) will be collected at baseline from all consenting participants. Collection of blood samples for genomics testing is voluntary. Should a participant not wish to provide a sample for this research, he/she will still be allowed to participate in the main study.

The Sponsor may only analyse samples from a subset of participants. Samples will be retained for as long as the quality of the material permits evaluation but not longer than 15 years or as per local regulations from the date of the last participant's last visit, after which they will be destroyed.

10.7.2 CCI

CCI

11 Statistics

11.1 Sample Size Calculation

A total of approximately 240 participants is considered sufficient to achieve the objectives of the trial. This number of participants will provide a precision of ±6.2% in the estimate of the proportion of participants achieving an EASI ≤7 at Week 24, which is expected to be approximately 60% (ie, 95% confidence interval [CI]=53.8%, 66.2%).

In a retrospective analysis of data from the pivotal trials, ADvocate 1 and ADvocate 2, approximately 60% of participants treated with lebrikizumab 250 mg Q2W achieved EASI ≤7 at 24 weeks.

11.2 Structure and Methodology of the Statistical Analysis

Statistical analyses of demographic, baseline characteristics, effectiveness, safety and tolerability data will be performed by the CRO Biostatistics department. A fully specified Statistical Analysis Plan (SAP) will be prepared by the CRO statistician under the CRO's SOPs prior to first participant enrolment. The Statistical Analysis System (version to be specified in the SAP) will be the statistical software used to analyse the data sets. A complete set of raw data listings will be appended to the Statistical Report. All tables, figures, and listings will be presented in portable document format (PDF) without any manual editing, ie, they will appear unmodified as programmed by means of the statistical package.

Full study results will be delivered once all participants have completed the study (Week 24) or discontinued from the study prior to this point.

Tables, figures, and listings will be compiled in the statistical report and appended to the CSR.

11.3 Analysis Populations

The following analysis sets are defined:

- The Full Analysis Set (FAS) includes all enrolled participants
- The Safety Analysis Set (SAF) includes all enrolled participants who received at least 1 dose of the trial drug

The analysis of all the effectiveness variable and patient- and Investigator-reported outcomes will be performed on the FAS population; all safety and CCI [redacted] analyses will be conducted using the SAF population.

11.4 Descriptive Statistics

Categorical variables will be summarised with counts (n) and percentages (%) and will be tabulated. For continuous variables, the number of non-missing observations (n), mean, standard deviation (SD), standard error (SE) of the mean, 95% CI of the mean, median, first (Q1) and third (Q3) quartiles, minimum (min) and maximum (max) will be tabulated. When applicable, these summaries will be provided by visit and time-point of assessment.

11.5 Participant Disposition

The number of participants included in each analysis set, the number of participants who complete the trial, the number of participants who discontinued, and the reasons for discontinuation will be summarised using descriptive statistics. Summaries of disposition will be based on the FAS.

11.6 Demographic and Baseline Characteristics

The trial population will be described using demographic and baseline characteristics recorded during the screening period. Analyses of demographic and baseline characteristics will be based on the FAS; additional populations may be analysed as appropriate.

Appropriate descriptive statistics according to Section 11.4 will be provided for the demographic and baseline characteristics. No statistical tests will be performed. Full details of the summaries to be produced will be provided in the SAP.

11.7 Endpoints

See Section 6.1 for a full listing of the study objectives and their associated endpoints. The estimands are detailed in Section 6.2 and summarised in Table 6 below. Any additional estimands will be described in the SAP.

Table 6: Summary on Study Estimands

Estimand	Intercurrent Event			Missing Data Imputation Method
	Treatment Discontinuation		Use of Prohibited Medication for AD	
	Due to Lack of Effectiveness	For Any Other Reason		
Estimand of the primary and secondary objectives (hybrid)	Composite: Set to baseline	Hypothetical: Set to missing	Treatment policy: Observed	MCMC-MI
Supportive estimand (hybrid)	Composite: Set to baseline	Hypothetical: Set to missing	Composite: Set to baseline	MCMC-MI

Abbreviations: AD=atopic dermatitis; MCMC-MI=Markov Chain Monte Carlo-multiple imputation

11.8 Statistical Methods

No inferential statistical analysis will be performed. Effectiveness, patient- and Investigator-reported outcome, safety, and CCI [redacted] will be summarised by means of descriptive statistics (see Section 11.4).

Subgroup analyses include but are not limited to prior exposure to dupilumab (yes/no), baseline disease severity (EASI score), and country.

11.9 Handling of Missing Data

Every effort will be made to prevent participants withdrawing from the study, and for participants who permanently discontinue study drug (and are not lost to follow-up) every effort will be made to continue to collect data after treatment discontinuation as outlined in Section 8.4.2.

For the estimand of the primary and secondary objectives, missing data including those as a result of ICE (see Section 6.2) will be imputed based on MCMC-MI as described in Table 6.

Further details on the handling of missing data and any sensitivity analyses will be provided in the SAP.

11.10 Multiplicity Strategy

Not applicable.

11.11 Interim Analysis

An interim analysis would allow a preliminary evaluation of assessments not previously performed in study participants treated with lebrikizumab, including the CCI , mTLSS, participant and Investigator satisfaction questionnaires, and CCI and CCI . Additionally, it would inform on clinical outcomes in patients previously treated with dupilumab.

An interim analysis (ie, based on a data cut-off) may be performed when approximately 100 participants have completed the study (Week 24), if relevant clinical information may be gained in a timely manner prior to the completion of the full study, depending upon the study recruitment rate. For example, in the event of rapid study recruitment (eg, full enrolment within 6 months or so), the conduct of an interim analysis may not be beneficial, as the interim results may not be received much in advance of study completion. The decision on the need for an interim analysis will be made once approximately 100 participants have completed Week 24, based on considerations of the anticipated time remaining before all participants have completed the study, and the decision will be documented in the Trial Master File.

12 Data Handling, Processing, and Record Keeping

The Investigator will conduct the trial in accordance with the protocol and International Council for Harmonisation (ICH) E6 GCP guidelines. In addition to the routine monitoring procedures, training records should be in place to ensure Investigators and CROs understand the data processing in any of the computerized systems to be used to ensure the confidence in the reliability, quality, and integrity of the participant data.

Sponsors, CROs, data safety monitoring boards, and other authorized personnel can view the trial data elements in the eCRF before and after the clinical Investigator(s) has electronically signed the completed eCRF. Reviewing trial data dynamically will allow early detection of trial-related problems (eg, safety concerns, protocol deviations) and problems with conducting the trial (eg, missing data, data discrepancies).

According to the eCRF entry guidelines, eCRFs must be completed for each participant by qualified and authorized personnel. Any data entry and corrections made on the eCRF must

have a respective audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the trial should be collected.

A list of all authorized data originators (ie, persons, systems, devices, and instruments) should be developed and maintained by the CRO and made available at each clinical site.

The eCRF is an auditable electronic record of information reported to the Sponsor on each trial participant, according to this clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed, managed, stored, analysed, and reported.

12.1 Data Collection

12.1.1 Identification of the Trial Data Sources

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation.

When a device or instrument is the data originator (eg, blood pressure monitoring device or glucometer) and data are automatically transmitted directly to the eCRF, the eCRF is the source.

Access to source data is critical to the review and inspections of clinical investigations. Source data should be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available (ALCOA+) and must meet the regulatory requirements for record keeping.

The trial data sources are outlined below:

- Signed ICFs
- Participant medical records will include: AD diagnosis and inclusion/exclusion criteria, age, gender, physical examination, previous medication, original or certified copy of a laboratory reports, instrument printouts, trial progress notes of the physician, reason for withdrawal, dose, contraception methods, and change in child bearing potential
- Effectiveness assessments:
  - Clinical signs: EASI, IGA, CCI [redacted] BSA, mTLSS, SCORAD
  - AD patient-reported symptoms: Pruritus NRS, Sleep-Loss Scale, POEM, CCI [redacted], CCI [redacted]
  - QoL and impact of disease: DLQI/CDLQI; CCI [redacted] and CCI [redacted]
- Safety assessments – AEs, physical examinations, clinical laboratory assessments (haematology, chemistry, and serum/urine pregnancy test for WOCBP).
- Blood sampling for genomics
- Blood sampling for CCI [redacted]
- Participant eDiaries

- eCRF

12.1.2 Electronic Case Report Forms

To comply with the requirement to maintain accurate case histories Investigators should review and electronically sign the completed eCRF for each participant before the data are archived or submitted. Use of electronic signatures must comply with United States Title 21 CFR part 11.

For trial data elements transcribed from paper or electronic to the eCRF, the electronic or paper documents from which the data elements are transcribed are the source.

These data must be maintained by the Investigators and available to the monitor or inspector if requested (eg, an original or certified copy of a laboratory report, instrument printout, progress notes of the physician, the trial participant's hospital chart(s), nurses' notes.

Direct Entry of Data Into the eCRF

Direct entry of electronic data coming from other electronic systems (ie, eDiary, electronic patient reported outcomes [ePRO], etc.) used for the trial will eliminate error transcription from manual data entry eCRF. For the following data elements, the eCRF is the source:

- Inclusion and exclusion criteria confirmation
- EASI, IGA, CCI BSA, SCORAD for Investigator, SCORAD, Investigator-Reported Satisfaction Questionnaire

  Note: Central laboratory portal is the source for laboratory results.
- Urine pregnancy test results

For the above trial data elements, the eCRF is the source. If a paper transcription step is used, then the paper documentation should be retained and made available for monitoring or inspection.

Direct data entry should be in compliance with ALCOA+. In case trial data cannot be entered at the time of the participant visit, eg, laboratory tests results, then Investigators are requested to make their entries at the time when the report with the results is received.

All non-CRF entered external data (eg, images, CCI , etc.) will not be loaded into the eCRF, but it will be integrated in SAS datasets and reconciled frequently with the eCRF data by the CRO Data Management (DM) group.

The source data verification will be performed by the CRO CRA/monitor according to the requirements specified in the Monitoring Plan.

At the trial end, the CRO will generate one certified "true copy" of the completed case report forms at site and will send to the Investigator(s) that copy certification together with the completed eCRFs (in PDF) from all participants enrolled at his or her location.

12.1.3 Participant Diary

A mobile application named the Study App will be used during the study. Research personnel will be instructed on the use of the Study App in order that they further instruct the participants

at the Baseline Visit and as many times as deemed necessary. Participants will also receive written instructions on the Study App use and reminders, including but not limited to, to complete the questionnaires and diary during the study, and treatment dosing.

The Study App data will be available for the site in real time through the Study App admin portal. The site will be able to follow the progress and compliance of the participant.

When an instrument is used by a participant or Investigator to transmit participant data elements directly to the eCRF, the participant or Investigator is the data originator and the eCRF is the source of data. If a process is used by which the participant or Investigator uses the instrument to transmit data to a technology service provider database, the service provider database is the source.

The Study App will allow participants to complete PRO questionnaires and a diary. The participants will be asked to have the Study App on their own mobile phone. There will also be the possibility to provide participants with a mobile phone, if necessary.

For this study, each participant will complete the following PROs through the ePRO module:

- Pruritus NRS
- POEM
- DLQI/CDLQI
- Sleep-Loss Scale
- CCI [redacted]
- CCI [redacted] and CCI [redacted]
- CCI [redacted]
- SCORAD (only those questions addressed to participants)

The Study App recording will be transferred to the database. The Study App will work across all smartphones and tablet operation systems.

At the study end the Investigator will receive a CD/DVD/USB with the mobile application data (in PDF) from the participants enrolled at his/her location. The Investigator will keep this CD/DVD/USB with the rest of the original data for as long as required by local regulations. The mobile application files are relevant documentation for registration.

The mobile app data is the sole property of the Sponsor and should not be available in any form to third parties without the written permission of the Sponsor, except to authorize representatives of appropriate Competent Authorities.

12.2 Data Management and Quality Control

Data Management of the trial will be performed by the CRO DM department and supervised by the Sponsor's DM department, according to the Sponsor templates and CRO SOPs.

To facilitate the collection of accurate and complete data, the CRO will target the risks associated to critical trial data and will be documented into the Data Management Plan (DMP) and the Monitoring Plan.

Investigators will respond within 48 hours or less as per the DM documents to any critical query generated by the DM group or any data risk indicator reported.

Main DM activities and procedures will be accurately described in the DMP, created by the CRO and sent to the Sponsor for review.

Database checks and listings will be programmed by the CRO, according to the Data Validation Plan document provided in the DMP. Database checks and listings programming will be appropriately validated by the CRO.

Reconciliation of trial data and SAEs between Clinical and Drug Safety databases will be performed by the CRO in ongoing basis and before database soft lock at the CRO. Procedures to be followed will be detailed in the DMP.

Encoding of specific data will be carried out by the CRO. For this trial, medical history, AEs, and concomitant medications will be coded; the Medical Dictionary for Regulatory Activities and WHODrug Global dictionaries will be used, version number of each dictionary will be documented in the DMP.

A Quality Control check to ensure the accuracy of the data will be done by the CRO, when data is cleaned on an ongoing basis and just before the database lock. Specifications of the Quality Control check will be found in the DMP.

An audit trail will be maintained to protect the authenticity and integrity of the clinical data.

12.3 Investigator's and Trial Master Files

The Investigator's file and Sponsor Trial Master File will contain all trial documents indicated in the ICH GCP guidelines and local regulations.

At the trial end the Investigator will receive one CD/DVD/USB drive with the EDC data, as well as one CD/DVD/USB drive with the electronic Participant Diary data from the participants enrolled at his/her location. The Investigator will keep these in the Investigator's file.

The Sponsor's Trial Master File will contain at a minimum all documents indicated in the ICH GCP guidelines. The documents needed in the Sponsor's file (originals and copies) generated or obtained by the CRO will be sent to the Sponsor following adequate time points and in the format defined by the Sponsor.

All records must be stored in a secure facility protected from fire, flood, and unauthorised access where they may be readily accessed in the event of an audit or inspection.

12.4 Documents and Record Keeping

The Investigator should retain control of the records (ie, completed and signed eCRF or certified copy of the eCRF). The Investigator maybe requested by inspectors with access to the records that serve as the electronic source data.

When data elements are transcribed from paper sources into an eCRF, the Investigator must also retain the paper sources, or certified copies, for later review. Other records (electronic and paper) required to corroborate data in the eCRF may also be requested during an inspection.

All trial data (including electronic data), all hard copies including protocol, consent forms, CRFs, queries and printouts, and all essential documents relating to the conduct of the clinical trial will be stored at the research site for a period of 25 years after completion of the trial, unless otherwise communicated in writing by the Sponsor.

CROs/vendors will store the databases, including audit trails and related documentation, for a period of 25 years after completion of the trial, 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.

13 Quality Control and Quality Assurance

13.1 Training of Staff

During the set-up phase of the trial, appropriate kick-off meetings will be performed between the Sponsor and the CRO and/or vendors (eg, eCRF, laboratories), to train CRO staff on trial procedures.

An Investigators' meeting will be held, including training on GCP procedures, trial protocol, effectiveness and safety assessments, laboratory procedures, eCRF completion, usage of any specific device and any other applicable process/procedure/method as applicable.

An initiation visit will be performed at each site by the trial CRA designated by the CRO to assess if all the material and supplies (eg, case report form, IMP) arrived in good conditions and to train the site staff for protocol compliance.

Appropriate Trial Manuals will be provided to the research sites as written help to support all trainings on all trial procedures (eg, laboratory samples, eCRF).

13.2 Monitoring

The trial will be monitored by the designated CRO according to the details specified in the Monitoring Plan.

The trial CRA/Monitor will conduct monitoring visits according to a pre-agreed schedule and with enough frequency to perform source data verification, check the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrolment and to ensure that trial medication is being stored, dispensed, and accounted for, according to specifications and report any deviation as soon as possible to the Clinical Trial Manager. The schedule can adapt to monitoring workload and/or prevailing circumstances at the site.

Standard monitoring reports will be produced by the trial CRA(s) after each visit and filed in the Trial Master File. Key trial personnel must be available to assist the CRA(s) during these visits.

The Investigator must also keep the original ICF signed by the participant (or parents/caregivers, if applicable) and maintain source documents for each participant in the trial, case and visit notes medical records, all information on case report forms must be traceable to these source documents in the participant's file.

A close out visit to solve pending issues and to agree on the shipment of remaining trial materials to the Sponsor (eCRF/CRFs and other data source, medication) will be performed by the trial CRA/Monitor once all participants have completed the trial.

13.3 Inspections and Audits

The trial site, trial processes, CRO, providers and/or trial documents may be subject to Quality Assurance audits by the Sponsor (or authorised partner companies) as well as inspection by the appropriate Competent Authorities during the trial or after trial completion. Audits and inspections may include, but are not limited to, drug supply, presence of required documents, ICF process, medical records, general protocol compliance and comparison of data recorded on the eCRF and queries against source documents. Investigator will ensure direct access to source medical records for inspection and audit purposes.

14 Ethics

This trial will be conducted in accordance with the recommendations guiding physicians in biomedical research involving humans adopted by the 18th World Medical Assembly of Helsinki (1964), as amended in Fortaleza, Brazil (2013), as well as in compliance with ICH GCP guidelines, and local laws of the countries in which the trial centres are located.

14.1 Responsibilities

The Investigator is responsible for conducting the trial in accordance with the procedures described in this protocol. All the personnel involved in the clinical trial will be fully informed about the drug and the nature of the trial and will be subject to protocol procedures concerning their duties in the trial.

The Investigator, the CRO/vendors and the Sponsor should ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance to the highest standards of Good Clinical Practice (ICH GCP guidelines) and local regulations.

The Investigator, the CRO and the Sponsor will work according to the ICH guidelines and the EU Clinical Trial Regulation 536/2014.

The Investigator shall administer the trial medication to participants under his or her personal supervision or under the supervision of any co-Investigator reporting to him/her who are identified in the delegation of responsibilities and signatures log. The Investigator and designees will be responsible for the participant's compliance throughout the trial.

At the completion of treatment (or premature discontinuation) participants will be instructed to resume the medication they were taking before starting the clinical trial, or any other as deemed appropriate by the Investigator. Medical care after discharge from the trial should be provided by the participant's family practitioner or specialist that usually treats his/her condition.

14.2 Participant Information and Informed Consent

As the first act of recruitment into the study, participants will be informed by the Investigator in detail of the characteristics of the drug to be administered, the nature of the clinical investigation, the risks and the discomfort that can reasonably be expected as a result of their participation and the uses of the data, as described in the Patient Information Sheet.

The participants will be informed that they are free to withdraw their consent and suspend their participation in the trial at any time with no penalty or loss of benefits to which the participant is otherwise entitled. Administration of the drug may be interrupted, and a participant withdrawn from the trial at the discretion of the Investigator. The Investigator should justify his decision in the participant's eCRF. Any retained samples from participants who withdraw consent will be destroyed.

Any participant considered by the Investigator to be suitable for inclusion must document his or her willingness to participate in the trial by giving his or her consent in writing before starting any trial procedure by signing the ICF/IAF, which must be dated by the participant and the Investigator. At such time the participant must be given adequate time to understand the information provided and ask questions, if required. Participants who are below the age of majority (ie, <18 years) at the Baseline Visit will be asked to give their assent to participate in the trial by signing the assent form, and their parent(s) or legal guardian must sign the ICF. A copy of the signed ICF/IAF will be given to the participant, parent(s), and/or legal guardian. The original(s) shall be kept on file by the Investigator. Any new relevant information that becomes available during the trial will be provided to the participant. If during the trial, a minor reaches the age of majority, his or her express informed consent shall be obtained through the signing of the ICF before that participant can continue to participate in the clinical trial.

The Patient Information Sheet and ICF/IAF will include all elements required according to the applicable legislation. These documents or any modification will have been authorized by the Sponsor and approved by the relevant IEC/IRB before use.

After the completion of the trial, lay summaries summarizing main results from the trial will be made available for participants.

14.3 Independent Ethics Committee or Institutional Review Board Review

This protocol, patient information, and the informed consent form should be submitted to an IRB or IEC for review and approval. Notification in writing of approval must be obtained from the EC by the Investigator before initiation of participant enrolment.

The Investigator/Sponsor or CRO (per regulations: ie, Investigator in the United States or Sponsor in the European Union) must promptly report to the IEC/IRB all changes in research (protocol amendments) and will not make such changes without IEC/IRB approval except where necessary to eliminate apparent immediate hazards to the trial participants or administrative changes.

Serious adverse events reasonably related to the trial drug will be communicated by the Investigator/CRO to the IEC/IRB.

Within 1 year after completion of the trial, the responsible person according to local regulations, Investigator/CRO will send to the IEC/IRB and to the Competent Authority a brief summary explaining the results obtained in the trial.

The Investigator/CRO is required to maintain accurate and complete records of all written correspondence sent to and received from the IEC/IRB and must agree to share these documents and any reports with the Sponsor.

14.4 Participant Data Protection

The trial participants shall be informed by the Investigator that complete confidentiality will be maintained concerning their identity. On eCRFs/EDC and all trial data records (eg, electronic participant diary) participants will be identified only by the assigned participant identification number and year of birth.

A signed written ICF signifies the explicit acceptance by the individual that data from the trial will be available to the Investigator and his/her staff, the authorized representatives of the Sponsor and, if required, by the IEC/IRB and Competent Authorities. However, all data contained in the participant's medical history will be considered as confidential. The Sponsor will treat data according to personal data Regulation (EU) 2016/679, and any other applicable national and international regulation.

All clinical trial findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The Sponsor has in place a program for personal data protection and prevention and management of Personal Data breaches: Policy PCG-24 (Personal Data Protection Policy); SOP-24/01 (Personal Data Management SOP), and a Protocol for Information Security Incident Management defining a procedure to properly manage and handle information security incidents, with or without impact on personal data, and the corresponding responsibilities, minimizing the potential damage and making sure all impacts are managed appropriately.

In case of data breach, the Sponsor shall be notified without undue delay, gathering as much information as possible to permit an assessment by its Data Protection Officer (DPO) in relation to whether the breach is likely to result in a high risk to the rights and freedoms of natural persons and to arrange any necessary measures to secure the data and to minimize any possible adverse consequences for data subjects, as applicable. Any data breach will pass through five phases of incident handling (Detection, Analysis, Response, Recovery, and Post-incident Management), involving different stakeholders. Depending on the nature of the breach an Incident Response Team will form, where the DPO shall participate to minimize the adverse impacts to data subjects. Depending on the nature and impact of the data breach, the DPO will notify supervisory authorities of the personal data breach without undue delay and, where feasible, no later than 72 hours, where applicable.

15 Financing and Insurance

The Sponsor will set up a contract with the CRO with the economic aspects for trial funding.

All participants recruited will have an insurance policy provided by the Sponsor to cover any possible risk resulting from their participation in the clinical trial.

Except in the proven case of clinical malpractice, the insurance company will indemnify against any claim or claims made by participants or their dependents which may result from administration of the IMP.

16 Publication Policy

The Sponsor will disclose clinical trials in a manner consistent with applicable national laws and rules governing personal data privacy and protection of intellectual property rights. Clinical trials will be registered, and results disclosed by means of recognized public databases, such as clinicaltrials.gov in the US and the Clinical Trial Information System (euclinicaltrials.eu) in the EU.

The Investigator understands and accepts that his/her name and trial centre may be disclosed in the context of this national or international legislation.

All the information related to this clinical trial is considered strictly confidential and is the property of the Sponsor. This information will not be given to a third party without the written consent of the Sponsor.

By signing this trial protocol, the Investigator affirms to the Sponsor that he/she will maintain in confidence all information furnished to him/her or resulting from this trial. The Investigator will only divulge such information as may be necessary to the IEC/IRB, the members of the staff, and the participants who are involved in this trial.

All relevant aspects regarding publication will be part of the contract (or similar document) between the Sponsor and CRO.

In all cases, the trial results shall be reported in an objective, accurate, balanced, and complete manner, with a discussion of the strengths and limitations of the trial. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication.

Publication and/or presentation whether complete or partial, of any part of the data or results of this trial will not be allowed until global publication and trial results disclosure by the Sponsor as per European Medicines Agency and/or US Food & Drug Administration regulatory compliance obligations, and only after mutual agreement between the Investigator and the Sponsor.

17 Other Practical Considerations

17.1 Summary of Product Characteristics

European marketing authorisation was granted for lebrikizumab on 16 November 2023 (EMEA/H/C/005894) for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy. In this study, lebrikizumab is used within the scope of this authorisation, thus the approved Summary of Product Characteristics (SmPC) serves as the clinical reference document. The Ebglyss® (lebrikizumab) SmPC provides details on the product identity and composition, clinical particulars including undesirable effects, and pharmacological and pharmaceutical properties.

17.2 Final Clinical Trial Report

The CSR will be written following the ICH guidelines requirements. It will be approved and signed by the Principal/Coordinating Investigators and the Sponsor's representatives according to internal SOPs.

The CSR will be audited by CRO and/or the Sponsor before issuing the final version.

The final version of electronic CSR will be e-published (hyperlink, bookmarks, etc.) including all appendices according to ICH Guidelines.

The summary of the CSR will be sent to all the Investigators participating in the clinical trial as well as to the IECs and/or Competent Authorities according to the local regulation.

17.3 Protocol Modifications

Modifications of the original protocol are referred to as "amendments" to the trial protocol. Modifications of the original protocol may only be made with the Sponsor's approval. Two types of amendment maybe produced:

- Substantial Amendments (related to the safety or physical or mental integrity of the participants, scientific value of the trial, conduct or management of the trial or the quality or safety of any IMP used) must be notified to the IEC/IRB and/or Competent Authorities and approved by them before implementation.
- Non-substantial Amendments do not require notification but should be recorded and be available on request for inspection at the trial site and/or Sponsor premises as appropriate.

17.4 Protocol Deviations

Any protocol deviations during the conduct of the trial will be recorded by CRA/Monitors as detected or derived from data collected in the clinical database.

Relevant deviations will be promptly reported to the Sponsor after detection. Important protocol deviations will be included in the corresponding listing of the CSR.

Additionally, protocol deviations will be reported to the IECs and/or Competent Authorities according to the local regulation in each country.

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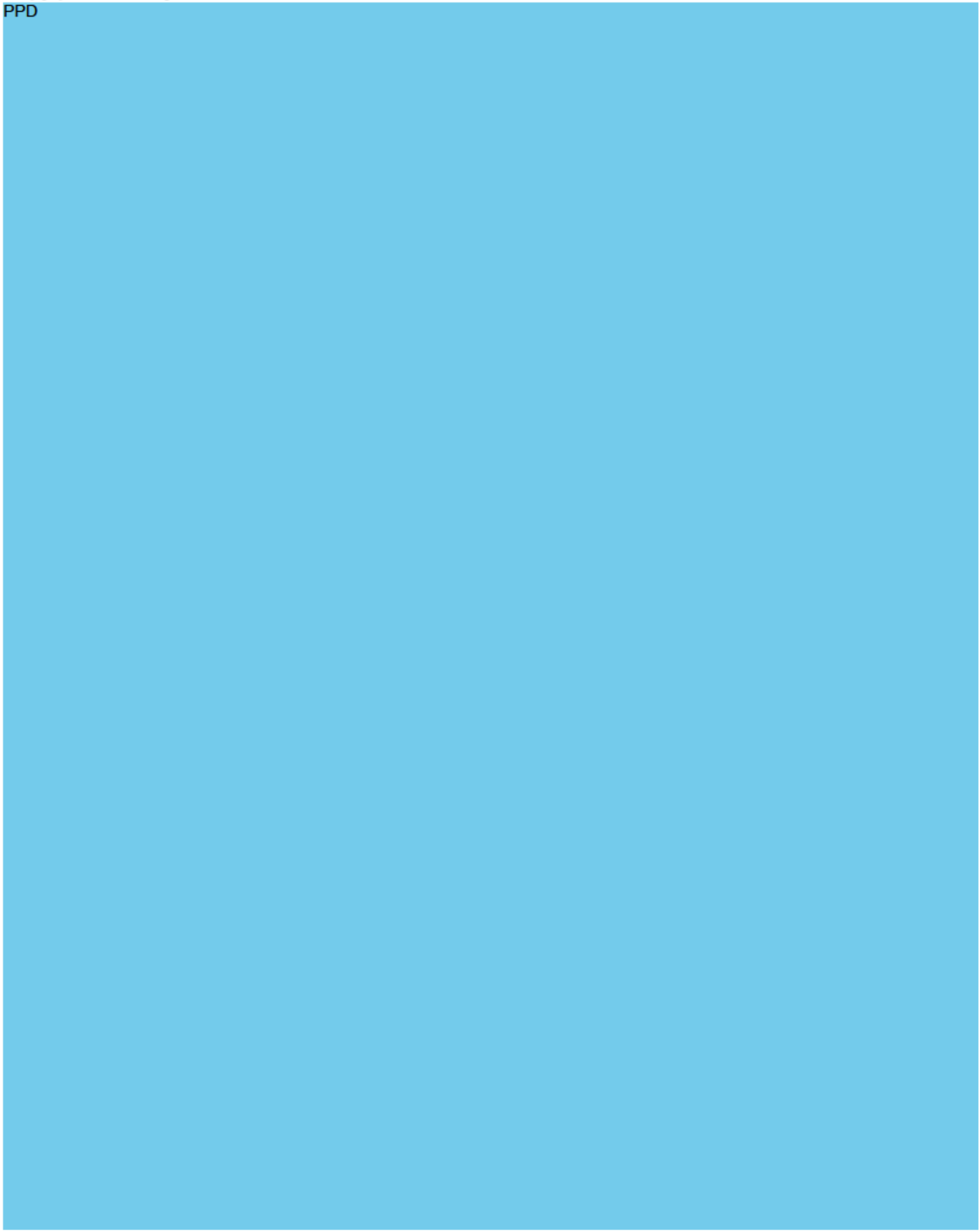

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To request paper copies from Almirall GXP

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to PPD and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Almirall GXP

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to PPD and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

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To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

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- Until or unless you notify Almirall GXP as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Almirall GXP during the course of your relationship with Almirall GXP.