ALMIRALL, S.A.

Clinical Trial Protocol M-17923-30

Clinical Trial Protocol Title:	A Randomised, Double-Blind, Placebo-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adult and Adolescent Patients With Moderate-To-Severe Atopic Dermatitis That Are Not Adequately Controlled With Cyclosporine or For Whom Cyclosporine is Not Medically Advisable.
Short Protocol Title:	Efficacy and safety of lebrikizumab in patients with atopic dermatitis (AD) not adequately controlled or non-eligible for cyclosporine
Investigational Medicinal Product(s):	Lebrikizumab
Indication:	Atopic Dermatitis
Development Phase:	Phase 3
Final Protocol Version Date:	3.0, 22 August 2022
Amendment(s)	**Number:** Global Amendment 2 **Date:** 22 August 2022 **Number:** Global Amendment 1 **Date:** 13 December 2021
EudraCT Number:	2021-002967-23
Sponsor:	Almirall, S.A. Ronda General Mitre, 151 08022 Barcelona, Spain

Protocol Amendment Summary of Changes

Amendment No.	Date	Summary of Changes	Rationale
Global Amendment 1	13 December 2021	This amendment provides an updated trial design of the 36-week open-label Maintenance Period, which will now have one treatment arm only (every 2 weeks regimen). Updated the statistical analysis plan accordingly. Removed every 4 weeks regimen and related details.	Limited ability to collect insights that would reflect clinical practice and limited current understanding of which patients can benefit from every 4 weeks dosing.
		CCI [redacted]	
		Added blood sample and urine sample (for haematology, biochemistry, and urinalysis) at Week 32 during the Maintenance Period and updated endpoints accordingly.	To more appropriately monitor the safety of patients during the Maintenance Period.
		Added Treatment Satisfaction Questionnaire for Medication-9 items assessments at Baseline during the Induction Period.	To evaluate patient's last treatment.
		Added that photography will be collected for the patients who consent at selected sites.	Added clarification for the collection of photography.
		Shortened the fasting period, alcohol consumption and strenuous physical activity from 12 to 8 hours.	Updated based on United Kingdom European Community recommendation.

Amendment No.	Date	Summary of Changes	Rationale
		Post-last dose follow-up period reviewed and increased from 12 to 18 weeks. Added urine pregnancy test follow-up every 4 weeks after last dose.	Consistent with lebrikizumab elimination half-life time ($t_{1/2}$).
		Removed urine pregnancy test from Screening.	To perform only serum beta-human chorionic gonadotropin at Screening.
		Updated number of trial centres and countries.	To add additional trial centres.
		Added upadacitinib and tralokinumab to sentence about newly approved treatments in background section.	To update recently approved new treatments for moderate-to-severe atopic dermatitis.
		Added statement about drug accountability if injection is done at home by patient or their caregiver.	To monitor patient compliance.
		Added statement that topical therapy, including TCS, should not be applied before the patient has undergone all study procedures and clinical evaluations on days of study visits.	To perform skin assessments properly.
		Updated assessment of comorbidities in medical history.	To further understand the impact of patient comorbidities in the efficacy or safety of lebrikizumab.
		Added section on COVID-19.	COVID-19-related measures per regulatory guidance.
		Removed Appendices 2 to 17 (efficacy and PRO scales; Fitzpatrick skin phototype scale).	To provide follow-up form separately to the sites.
		Nonsubstantial changes for administrative, typographical, and/or grammatical corrections throughout the document.	
Global Amendment 2	10 August 2022	This amendment provides an update to the biostatistical portions, including:	

Amendment No.	Date	Summary of Changes	Rationale
		- Change of focus for primary analysis to Overall Population (instead of Dupilumab Naïve)	- Because of the results of Phase III study (ADhere) with the dupilumab naïve population, which did not confirm the initial assumptions for the study sample size calculation.
		- Estimand framework amended to match that of Phase III Lebrikizumab study	- To provide a comparable framework to the Phase III studies (Advocate 1 and Advocate 2).
		- Odds ratio added to CMH analyses	- To provide a more complete assessment of response (in addition to risk difference)
		- QoL analyses split out to provide clearer definition of analyses	- For clarity
		- Missing data Section 11.10 updated in line with Phase III Lebrikizumab study, corresponding to updates to estimands framework.	- To provide a comparable framework to the Phase III studies (Advocate 1 and Advocate 2).
		Nonsubstantial changes for administrative, typographical, and/or grammatical corrections throughout the document.	

Sponsor Signatures

Clinical Trial Protocol Title:	A Randomised, Double-Blind, Placebo-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adult and Adolescent Patients With Moderate-To-Severe Atopic Dermatitis That Are Not Adequately Controlled With Cyclosporine or For Whom Cyclosporine is Not Medically Advisable.
Trial Code:	M-17923-30

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 Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and to local regulatory requirements, wherever applicable.

Sponsor

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

Functional Role	**Name**
PPD	PPD
PPD	PPD
PPD	PPD
This document was signed electronically in the eDMS R&D system. Manifestation of the e-signatures is available at the end of this document which are equivalent to handwritten signatures.	

Principal Investigator Signature

Clinical Trial Protocol Title:	A Randomised, Double-Blind, Placebo-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adult and Adolescent Patients With Moderate-To-Severe Atopic Dermatitis That Are Not Adequately Controlled With Cyclosporine or For Whom Cyclosporine is Not Medically Advisable.
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The individual signing this clinical trial protocol declares that he/she has reviewed it for completeness, accuracy. He/she is responsible for the trial and agrees to conduct it in adherence to the present document, any amendments, to ICH GCP guidelines, and to local regulatory requirements, wherever applicable.

Principal Investigator

Role	Name	Signature	Date
Principal Investigator	PPD		

1 Protocol Synopsis

Title:

A Randomised, Double-Blind, Placebo-Controlled Phase 3 Clinical Trial to Assess the Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adult and Adolescent Patients With Moderate-To-Severe Atopic Dermatitis That Are Not Adequately Controlled With Cyclosporine or For Whom Cyclosporine is Not Medically Advisable.

Short Title:

Efficacy and safety of lebrikizumab in patients with atopic dermatitis (AD) not adequately controlled or non-eligible for cyclosporine.

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 study report.

Trial Centres:

This is an international multicentre study. The study is planned to be conducted at approximately 81 centres in approximately 9 countries within Europe, including the United Kingdom, Italy, France, Spain, Germany, the Netherlands, Belgium, Austria, and Poland.

Study Duration:

The duration of the entire study from first patient, first visit to last patient, last visit is anticipated to be approximately 24 months.

Duration of Treatment:

The duration of each patient's treatment is up to 52 weeks. The study has 2 treatment periods: a 16-week double-blind Induction Period followed by a 36-week open-label Maintenance Period.

Duration of Patients' Participation in the Trial:

The total duration of each patient's participation in the trial, including Screening, treatment, and follow-up periods, is estimated at a maximum of 72 weeks (up to 4 weeks of Screening, 52 weeks of treatment [last dose given at Week 50], and 18 weeks of post-last dose safety follow-up).

Phase of Development:

This is a phase 3 trial.

Rationale:

Atopic dermatitis is a chronic inflammatory heterogeneous skin disorder characterised by recurrent eczematous lesions, intense itch, and skin pain (eg, discomfort or soreness). AD is one of the most common inflammatory skin disorders, affecting up to 20% of children and 10% of adults in high-income countries.[1]

The use of lebrikizumab for AD is supported by numerous preclinical studies demonstrating that AD is characterised by the increased expression of interleukin (IL)-13 in skin. Moreover, 3 clinical trials (summarised in Section 5.1.4) with lebrikizumab demonstrated significant clinical benefit in patients with AD.

Lebrikizumab is a humanised monoclonal immunoglobulin (Ig) G4 antibody which binds specifically to soluble human IL-13 with high affinity and potently inhibits IL-13 signalling through the IL-4Rα/IL-13Rα1 complex. A phase 3 programme is currently ongoing aimed at confirming safety and efficacy of lebrikizumab in patients with moderate-to-severe AD who are candidates for systemic therapy.

The current study aims to evaluate the efficacy and safety of lebrikizumab with concomitant topical corticosteroids (TCS) in patients with AD and a history of inadequate response or intolerance to cyclosporine A (CsA), or CsA-naïve patients for whom CsA treatment is not medically advisable.

Objectives:

This study is designed to evaluate efficacy and safety of lebrikizumab with concomitant TCS through Week 52 in adults and adolescents (aged ≥12 to <18 years and weighing ≥40 kg) with moderate-to-severe AD, who are not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable.

Primary

- To evaluate the efficacy of lebrikizumab compared with placebo in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 16.

Secondary

- To evaluate the efficacy in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable between Week 16 up to Week 52;
- To evaluate the safety and tolerability of lebrikizumab in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 16;
- To evaluate the safety and tolerability of lebrikizumab in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 68.

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Trial Design:

This is a randomised, double-blind, placebo-controlled, parallel-group study, 72 weeks in duration (up to 4 weeks of Screening, 52 weeks of treatment [last dose given at Week 50], and

18 weeks of post-last dose safety follow-up). The study is designed to confirm the efficacy and safety of lebrikizumab administered concomitantly with TCS in adolescents and adults with moderate-to-severe AD not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable.

The study has 2 treatment periods: a 16-week double-blind Induction Period followed by a 36-week open-label Maintenance Period. The study will be double-blind until Week 18 and open-label from Week 20 onward. The patients who received placebo during the Induction Period will receive loading doses of lebrikizumab at Weeks 16 and 18. To maintain blinding at Weeks 16 and 18, all patients will receive 2 injections at Weeks 16 and 18 (either 2 injections of lebrikizumab or 1 injection of lebrikizumab and 1 injection of placebo). From Week 20 onward, all patients will receive 1 injection of lebrikizumab 250 mg every 2 weeks (Q2W).

Number of Patients:

A sufficient number of patients will be screened to randomise approximately 312 patients with moderate-to-severe AD.

Trial Population:

Eligible adult and adolescent (aged ≥12 to <18 years and weighing ≥40 kg) patients with moderate-to-severe AD for at least 1 year, defined according to the Hanifin and Rajka Criteria,[2] an Eczema Area and Severity Index score (EASI) of ≥16, an Investigator Global Assessment (IGA) score of ≥3 and a body surface area (BSA) affected by AD of ≥10% will be enrolled (adolescent patients aged ≥12 to <18 years will make up 12.5% of the overall population compared to adults aged ≥18 years). Eligible patients must have documented history of inadequate response to treatment with topical AD medication within 6 months before Screening, documented history of inadequate response or intolerance to CsA, or CsA-naïve patients for whom CsA treatment is not medically advisable. Patients with previous exposure to dupilumab, including suboptimal responses (eg, persistence of itch despite treatment with dupilumab, flare-up days before the next dupilumab dose) may be included in the study with a washout period of 8 weeks before Baseline. During this washout period, patients may be allowed to use TCS, which will need to be stopped at least 1 week before Baseline. The enrolment of this subpopulation of patients will be limited to a maximum of 60 enrolled patients. All other enrolled patients must be naïve to IL-4 or IL-13 blocking antibodies.

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

Substance code/name:	Lebrikizumab
Administration route:	Subcutaneous (SC)
Unit dose/strength:	Each prefilled syringe is intended for a single 2 mL dose (250 mg)
Dosage form:	Solution for injection containing 125 mg/mL lebrikizumab. Supplied as a sterile prefilled syringe with a pre-assembled needle safety device (PFS-NSD).
Frequency:	During the 16-week Induction Period and 36-week Maintenance Period, 250 mg lebrikizumab Q2W (with loading doses of 500 mg [2 syringes] given at Baseline and Week 2 during Induction Period, and at Week 16 and Week 18 during the Maintenance Period for patients who

received placebo during the Induction Period). After completion of the Week 16 visit, patients will enter the Maintenance Period:

- Patients who received lebrikizumab 250 mg Q2W during the Induction Period will continue to receive lebrikizumab 250 mg Q2W during the Maintenance Period
- Patients who received placebo Q2W during Induction Period will start receiving lebrikizumab 250 mg Q2W (with loading doses at Week 16 and Week 18) during the Maintenance Period.

Placebo Product, Dosage, and Mode of Administration:

Substance code/name:	The placebo solution is identical in appearance and volume to the active solution except that it does not contain lebrikizumab
Administration route:	SC
Unit dose/strength:	Each prefilled syringe is intended for a single 2 mL dose
Dosage form:	Solution for injection, containing the same excipients as the respective active lebrikizumab. Supplied as a sterile prefilled syringe with a PFS-NSD
Frequency:	Placebo will be administered during the initial 16-week period (and at Weeks 16 and 18, if applicable) to maintain blinding. Placebo will be administered Q2W (loading dose, 2 syringes, will be given at Baseline and Week 2)

To allow patients in the placebo arm to receive lebrikizumab loading doses during the Maintenance Period, the blinding will be maintained in Week 16 and Week 18. In order to maintain the double-blind, patients from the lebrikizumab 250 mg Q2W arm will be administered a second injection of blinded placebo during Week 16 and Week 18. From Week 20 onwards, all patients will receive 1 injection of lebrikizumab 250 mg Q2W. Therefore, the study will be open-label from Week 20 onward.

Methodology:

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

Statistical Methods

Sample Size Calculation

The study is designed to gain an estimate of the effect of study treatment in the patient population of adults and adolescent patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable. The sample size for this study has been estimated to allow power enough to show efficacy in the overall study population for the primary and key secondary endpoints.

In the overall population, a total sample size of 312 patients, in a 2:1 ratio (208 lebrikizumab arm and 104 placebo arm) will provide more than 95% nominal power to detect a statistically significant difference of 25% (55% lebrikizumab arm versus 30% placebo arm) in the primary study endpoint: proportion of patients achieving EASI 75 at Week 16. As reference and considering independence between variables, this same sample size will provide more than 90% overall power to also detect a difference of 18% (30% lebrikizumab arm versus 12% placebo arm) in the proportion of patients achieving IGA (0/1) at Week 16 and of 34% differences (43% lebrikizumab arm versus 9% placebo arm) in the proportion of patients achieving a 4-point pruritus numerical rating scale (NRS) decrease from Baseline at Week 16.

Analysis Populations:

The following analysis sets are defined:

- The Full Analysis Set (FAS) includes all randomised patients. Patients will be analysed under the treatment group as randomised.
- The Per Protocol Analysis Set (PPS) includes all randomised patients who receive at least one dose of the study drug, have at least one post-Baseline EASI assessment, and additionally for whom there are no important protocol deviations affecting efficacy at Week 16. Patients will be analysed under the treatment group as randomised.
- The Safety Analysis Set (SAF) includes all randomised patients who receive at least 1 dose of the study drug. Patients will be analysed under the treatment group actually received.

The main analysis of all the efficacy variables will be performed on the FAS population. The primary and key secondary efficacy variables will also be analysed for the overall population using the PPS population to assess the robustness of the findings from the FAS population. All safety analyses will be conducted using the SAF population.

Statistical Analysis

Study results will be delivered in 2 parts: the first results delivery will be provided after the first database lock, once all patients have completed the Induction Period or discontinued study before this point, and the second results delivery will be provided after second database lock, at the end of the study (EOS), once all patients have completed the study, or discontinued before EOS.

Accordingly, 2 different database locks will be performed, and 2 different clinical study reports will be generated.

All endpoints described in Section 6 will also be analysed by previous exposure to dupilumab (Yes/No) as CCI

Demographics and Baseline Characteristics

Appropriate descriptive statistics will be used to summarise demographic and baseline characteristics, including but not limited to sex, age, region, race, height, weight, body mass index (BMI), skin type (Fitzpatrick scale[3]), and prior use of dupilumab. For stratification factors, both the factor as randomised and the actual factor will be summarised, if differences exist. Medical history information will be presented in a by-patient listing.

Efficacy Analysis

The primary efficacy endpoint, EASI 75 at Week 16, will be analysed by means of a Cochran-Mantel-Haenszel (CMH) model adjusted by country, age (adolescents/adults), prior use of dupilumab (yes/no), and baseline severity of disease (IGA=3/IGA=4). If the model does not converge, country will be removed as an adjusting factor. The estimate of the adjusted common risk difference, with corresponding Mantel-Haenszel-Sato (Sato 1989)[58] adjusted 2-sided 95% confidence interval (CI) and p-value will be presented. Additionally, the CMH adjusted odds ratio along with the 95% two-sided asymptotic CI will be presented in a similar manner to the primary analyses. The primary analysis will be based on the Full Analysis Set (FAS) which was defined as all randomized patients. When analysing the dupilumab naïve and previously exposed populations, the factor for prior use of dupilumab will be removed from the CMH adjustment.

Further details on sensitivity and supportive measures, including descriptions of all estimands, intercurrent events (ICEs) and handling approaches are included in Section 11.8.1.1. Details regarding imputation of missing data are included in Section 11.10.

Key secondary efficacy endpoints will be analysed in the same manner as the primary efficacy endpoint, on the same main and second estimands.

The binary secondary and other efficacy endpoints will be analysed using the same methodology as described above for the primary efficacy endpoint using only the main estimand.

Continuous secondary and other efficacy endpoints assessed at multiple post-Baseline visits during the Induction Period will be analysed for the main and second estimands for continuous endpoints by means of a mixed effect model for repeated measures (MMRM). More details are given in Section 11.8.1.1.

Time-to-event (TTE) endpoints will be analysed using Kaplan-Meier survival analysis methods. If available, for descriptive purposes, the estimate of the median time-to-event (in weeks) and the 2-sided 95% CI will be presented. A comparison of the survival distribution curves for the 2 treatment groups will be made by means of the log-rank test. The Cox proportional hazards model will be used to estimate the hazard ratio and its 95% CI of lebrikizumab compared with placebo at the respective time point. The main Cox proportional hazards model will include treatment group, with country, age, baseline disease severity, and previous exposure to dupilumab (when the overall population is analysed) as factors.

Quality of Life (QoL) endpoints of Total DLQI and CDLQI will be analysed in the same way as the continuous other secondary efficacy endpoints occurring at multiple post-Baseline visits, on the overall population. DLQI-R, RECAP, TSQM-9, and WHO-5 will all be analysed descriptively on the overall population. Any individual components related to QoL scoring will also be analysed descriptively for the overall population.

All efficacy and QoL variables for the Maintenance Period will be analysed by means of descriptive statistics and presented by treatment group as randomised during the Induction Period.

Safety Analysis

The analyses of safety and tolerability outcomes will be performed on the SAF.

Safety outcomes include AEs, vital signs (including body temperature, respiratory rate, pulse, and systolic and diastolic blood pressure), physical examinations (including application site reactions), and clinical laboratory assessments (haematology, chemistry panel, urine testing, and urine pregnancy test for women of childbearing potential).

All reported AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities. Details on the analysis of safety and tolerability endpoints are provided in Section 11.8.4.

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Interim Analysis

No interim analyses are planned.

Table 1. Schedule of Assessments (SoA)

Screening and Induction Period

Study Procedures	Screening	Induction Period[a]								
Study visit	1	2	3	4	5[b]	6	7[b]	8	9[b]	10
Day/Week (W)	W -4 to Day -1	Day 1-Baseline	W2	W4	W6	W8	W10	W12	W14	W16[c]
Visit window[d]			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Virtual visit (as per patient and Investigator preference)					☎		☎		☎	
Informed consent form/informed assent form	X									
Fitzpatrick scale	X									
Inclusion and exclusion criteria	X	X								
Demographics and medical history	X	X								
Review of immunisation record (for adolescents)	X									
Randomisation		X								
Vital signs	X	X	X	X		X		X		X
Physical examination and height, weight, and BMI measurement	X[e]									X
AEs	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X
Serology (HIV, hepatitis B and C) and coagulation (aPTT, PT, INR)	X									
Haematology and chemistry[f]	X									X
Urinalysis	X									X
Pregnancy test and contraception check[g]	X[h]	X[h]		X[h]		X[h]		X[h]		X[h]
Predose biomarkers blood sample		X								X
IGA, EASI, and BSA[i]	X	X	X	X		X		X		X
SCORAD[i]		X				X				X
Dispense eDiary	X									
Train/check understanding of recording data in the eDiary	X	X	X	X	X	X	X	X	X	X
Pruritus NRS[i,j], Sleep-loss scale[i,k], Skin Pain NRS[i,k]	X	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]

Study Procedures	Screening	Induction Period[a]								
Study visit	1	2	3	4	5[b]	6	7[b]	8	9[b]	10
Day/Week (W)	W -4 to Day -1	Day 1-Baseline	W2	W4	W6	W8	W10	W12	W14	W16[c]
Visit window[d]			±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
POEM, RECAP[i]		X		X		X		X		X
DLQI or CDLQI, DLQI-R[i]		X	X	X		X		X		X
WHO-5[i]		X								X
TSQM-9[i]		X								X
Photography[l]		X	X	X		X				X
Training autoinjection			X	X						
Administer study drug and Product Complaint reporting		X	X	X	X	X	X	X	X	X
Assess treatment compliance[m]			X	X	X	X	X	X	X	X

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BMI = body mass index; BSA = body surface area; CDLQI = Children Dermatology Life Quality Index; d = day; DLQI = Dermatology Life Quality Index; DLQI-R = DLQI-Relevant; EASI = Eczema Area and Severity Index; eDiary = electronic diary; HIV = human immunodeficiency virus; hCG = human chorionic gonadotropin; IGA = Investigator's Global Assessment; INR = International Normalised Ratio; NRS = Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure; PT = Prothrombin time; Q2W = every 2 weeks; RECAP = Recap of Atopic Eczema; SCORAD = Scoring Atopic Dermatitis; TCS = topical corticosteroids; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9 items; W = week; WHO-5 = World Health Organisation-Five Well-Being Index; WOCBP = women of childbearing potential.

a. A safety follow-up will occur 18 weeks after last dose of study medication (including both end-of-treatment period or after early termination).
b. Visits shaded in blue may be conducted remotely or on-site, per preference of the study site or patient. W68 will be on-site for WOCBP only.
c. For patients who received placebo during the Induction Period, loading doses of lebrikizumab will be given at W16 and W18 during the Maintenance Period. In order to maintain the double-blind, patients from the lebrikizumab 250 mg Q2W arm will be administered a second injection of blinded placebo during W16 and W18. From W20 onwards, all patients will receive 1 injection of lebrikizumab 250 mg Q2W.
d. Visit window for patient-reported outcomes is -3 days during Induction Period and -5 days during Maintenance Period.
e. For adults, height should only be captured at Screening. For adolescents, height should only be captured at Screening and Week 52.
f. Patients should attend the visit fasted. Patients should not eat or drink anything except water for 8 hours before sample collection. Alcohol consumption will not be permitted for at least 8 hours before visits. Strenuous physical activity should be avoided for at least 8 hours before a visit.
g. The contraception check is to confirm that contraception, if required, is used consistently and correctly.
h. Serum beta-hCG at Screening. Urine pregnancy test 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. For WOCBP, urine pregnancy tests will be conducted every 4 weeks after last dose of study medication (W54, W58, and W62) and at W68. Male subjects engaged in a relationship with a WOCBP must be contacted every 4 weeks after last dose of study medication (W54, W58, and W62) and at W68 to ensure respect of the contraception.
i. Patient-reported outcomes and quality of life measurements should all be completed before other study assessments. Assessments/procedures should be conducted in the following order: 1) patient-reported outcomes; 2) Investigator assessments and other efficacy assessments; 3) safety and laboratory assessments (including sample

collection for biomarkers); and 4) administration of study drug. Completed eDiary entries for Pruritus NRS and sleep-loss scales are needed for a minimum of 4 out of 7 days in the week preceding randomisation visit.

j. To be performed daily up to W2, weekly from W2 to W16, and every 2 weeks from W16 onward.
k. To be performed daily up to W2, weekly from W2 to W16, and every 4 weeks from W16 onward.
l. For patients who consent at selected sites.
m. Compliance assessment for study drug, TCS, as well as accountability.

Maintenance Period and Safety Follow-up

Study Procedures	Maintenance Period																		Safety Follow-up Visit[a]
Study visit	11	12	13[b]	14	15[b]	16	17[b]	18	19[b]	20	21[b]	22	23[b]	24	25[b]	26	27[b]	28	29[b]
Day/Week (W)	W18[c]	W20	W22	W24	W26	W28	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48	W50	W52/EoT	W68[a]
Visit window[d]	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
Virtual visit (as per patient and Investigator preference)			☎		☎		☎		☎		☎		☎		☎		☎		☎
Vital signs		X		X		X		X		X		X		X		X		X	
Physical examination, height, weight, BMI								X										X[e]	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology, chemistry[f]								X										X	
Urinalysis								X										X	
Pregnancy test, contraception check[g]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]	X[h]
IGA, EASI, BSA[i]		X		X		X		X		X		X		X		X		X	
SCORAD[i]								X										X	
Train/check understanding of recording data in the eDiary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pruritus NRS[i,j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Skin Pain NRS[i,k]; Sleep-loss scale [i,k]		X		X		X		X		X		X		X		X		X	
E-Diary: POEM, RECAP[i]								X										X	
DLQI or CDLQI, DLQI-R[i]				X				X										X	
WHO-5[i]								X										X	
TSQM-9[i]								X										X	
Photography[l]								X										X	
Administer study drug and Product Complaint reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Procedures	Maintenance Period																		Safety Follow-up Visit[a]
Study visit	11	12	13[b]	14	15[b]	16	17[b]	18	19[b]	20	21[b]	22	23[b]	24	25[b]	26	27[b]	28	29[b]
Day/Week (W)	W18[c]	W20	W22	W24	W26	W28	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48	W50	W52/EoT	W68[a]
Visit window[d]	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
Assess treatment compliance[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Abbreviations: AE = adverse event; BMI = body mass index; BSA = body surface area; CDLQI = Children Dermatology Life Quality Index; d = day; DLQI = Dermatology Life Quality Index; DLQI-R = DLQI-Relevant; EASI = Eczema Area and Severity Index; eDiary = electronic diary; EoT = end-of-treatment; HIV = human immunodeficiency virus; hCG = Human chorionic gonadotropin; IGA = Investigator's Global Assessment; NRS = Numerical Rating Scale; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; RECAP = Recap of Atopic Eczema; SCORAD = Scoring Atopic Dermatitis; TCS = topical corticosteroids; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9 items; W = week; WHO-5 = World Health Organisation-Five Well-Being Index; WOCBP = women of childbearing potential.

a. A safety follow-up will occur 18 weeks after last dose of study medication (including both end-of-treatment period or after early termination).
b. Visits shaded in blue may be conducted remotely or on-site, per preference of the study site or patient. W68 will be on-site for WOCBP only.
c. For patients who received placebo during the Induction Period, loading doses of lebrikizumab will be given at W16 and W18 during the Maintenance Period. In order to maintain the double-blind, patients from the lebrikizumab 250 mg Q2W arm will be administered a second injection of blinded placebo during W16 and W18. From W20 onwards, all patients will receive 1 injection of lebrikizumab 250 mg Q2W.
d. Visit window for patient-reported outcomes is -3 days during Induction Period and -5 days during Maintenance Period.
e. For adults, height should only be captured at Screening. For adolescents, height should only be captured at Screening and Week 52.
f. Patients should attend the visit fasted. Patients should not eat or drink anything except water for 8 hours before sample collection. Alcohol consumption will not be permitted for at least 8 hours before visits. Strenuous physical activity should be avoided for at least 8 hours before a visit.
g. The contraception check is to confirm that contraception, if required, is used consistently and correctly.
h. Serum beta-hCG at Screening. Urine pregnancy test 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. For WOCBP, urine pregnancy tests will be conducted every 4 weeks after last dose of study medication (W54, W58, and W62) and at W68. Male subjects engaged in a relationship with a WOCBP must be contacted every 4 weeks after last dose of study medication (W54, W58, and W62) and at W68 to ensure respect of the contraception.
i. Patient-reported outcomes and quality of life measurements should all be completed before other study assessments. Assessments/procedures should be conducted in the following order: 1) patient-reported outcomes; 2) Investigator assessments and other efficacy assessments; 3) safety and laboratory assessments (including sample collection for biomarkers); and 4) administration of study drug. Completed eDiary entries for Pruritus NRS and sleep-loss scales are needed for a minimum of 4 out of 7 days in the week preceding randomisation visit.
j. To be performed daily up to W2, weekly from W2 to W16, and every 2 weeks from W16 onward.
k. To be performed daily up to W2, weekly from W2 to W16, and every 4 weeks from W16 onward.
l. For patients who consent at selected sites.
m. Compliance assessment for study drug, TCS, as well as accountability.

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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
BOCF	Baseline Observation Carried Forward
BSA	Body Surface Area
CI	Confidence interval
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran Mantel Haenszel
CRA	Clinical Research Associate
CRO	Clinical Research Organisation
CsA	Cyclosporine A
CSR	clinical study report
DLQI	Dermatology Quality of Life Index
DLQI-R	DLQI-Relevant
DM	Data Management
DMP	Data Management Plan
EASI	Eczema Area and Severity Index Score
EASI 50	50% reduction from baseline in the EASI score
EASI 75	75% reduction from baseline in the EASI score
EASI 90	90% reduction from baseline in the EASI score
eCRF	Electronic Case Report Form
eDiary	electronic diary
EMA	European Medicines Agency
EOS	end of study
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
IAF	Informed Assent Form
IB	Investigator's Brochure
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
IMP	investigational medicinal product
IV	intravenous
IWRS	interactive web response system
JAK	Janus kinase
MCMC MI	Markov Chain Monte-Carlo Multiple Imputation
MMRM	Mixed Effect Model for Repeated Measures
NRI	Non-responder imputation
NRS	Numerical Rating Scale
OR	Odds Ratio
PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PPS	Per Protocol (Analysis) Set
PRO	Patient-Reported Outcome
PT	preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QoL	Quality of life
RECAP	Recap of atopic eczema
RNA	ribonucleic acid
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SFU	Safety follow-up
SoA	Schedule of Assessments
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TCS	Topical corticosteroids
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9 items
TEAE	Treatment-emergent adverse event
Th1	type 1/T-helper
Th2	Type 2/T-helper
US	United States

WHO-5	World Health Organisation - Five Well-Being Index
WOCBP	Women of childbearing potential

4 Sponsor, Investigator(s) and Trial Administrative Structure

4.1 Sponsor

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

Almirall Research and Development Centre:
Laureà Miró, 408-410
08980 Sant Feliu de Llobregat
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 from among the participating sites. The name, address, and affiliation of each Principal Investigator and the Coordinating Investigator will be detailed in the final clinical study report (CSR).

4.3 Administrative Structure

Medical Expert appointed by the Sponsor for this trial:

PPD

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 of the chemistry, pharmacology, efficacy, and safety of lebrikizumab is provided in the Investigator's Brochure (IB).

5.1 Background Information

5.1.1 Indication

AD is a chronic inflammatory heterogeneous skin disorder characterised by recurrent eczematous lesions, intense itch, and skin pain (eg, discomfort or soreness). AD is one of the most common inflammatory skin disorders, affecting up to 20% of children and 10% of adults in high-income countries.[1]

AD features activation of type 2/T-helper (Th2) immune responses and an altered skin barrier and skin microbiome.[4-7] Genetic studies of AD[8-11] have shown that genes encoding for type 2 cytokines involved in the regulation of the immune system (interleukin [IL]-4, IL-5, and IL-13) are strongly associated with the development of AD.[12-15] Type 2 cytokines increase epidermal

thickening, sensitisation, inflammation, and pruritus and decrease the expression of antimicrobial peptides and the barrier proteins filaggrin, loricrin, and involucrin. IL-13 in particular can reduce epithelial integrity and barrier function through downregulation of filaggrin, loricrin, and involucrin[16] and can act on keratinocytes in the skin to downregulate their differentiation.[17] IL-13 also induces T-cell chemoattractants that mediate T-cell infiltration into AD lesions[18] and may also induce IL-5 expression and eosinophil infiltration through the induction of eosinophil chemoattractants.[19] Increased expression of IL-13 has consistently been reported in AD skin lesions and is associated with disease severity.[20-26] 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.

In many patients, treatment with topical corticosteroids (TCS) provides some measure of symptomatic relief but does not always adequately control the disease. For patients with inadequate response or intolerance to topical therapies, guidelines recommend systemic immunosuppressants (eg, cyclosporine A [CsA], corticosteroids, methotrexate, azathioprine, or mycophenolate-mofetil), although these treatments show variable efficacy/effectiveness and tolerability and may be complicated by adverse effects and adverse medication interactions both in the short and long term.[27-31] Phototherapy is also recommended, but cannot be used as long-term treatment and has risks including burning, skin ageing, adverse medication interactions, and skin cancer.

Unlike other systemic immunosuppressants, CsA is approved in EU countries for severe AD when systemic therapy is required. CsA suppresses type 1/T-helper (Th1), Th2, and types 17 and 22 T-helper (Th17/22) cells, affecting both humoral and cellular immune responses.[32,33] Although off-label use beyond 1 year has been reported, long-term use of CsA (eg, beyond 1 year), as may be required in AD given the chronicity of the disease, is limited by risk of side effects.[34-36] Side effects associated with CsA include hypertension, nephrotoxicity, and subjective side effects (eg, headache, paraesthesia in fingers and toes, fatigue). Its use is also limited by contraindications because of other medical conditions or concomitant therapies. Dupilumab, an anti-IL-4R monoclonal antibody, was approved in 2017 for the treatment of adult and adolescent patients with moderate-to-severe AD.[37] More recently, a number of new treatments for moderate-to-severe AD have been authorised in Europe, namely baricitinib and upadacitinib (both oral Janus kinase [JAK] inhibitors) and tralokinumab (anti–IL-13 monoclonal antibody for subcutaneous injection). However, significant unmet medical needs remain because of the chronicity and heterogeneity of the disease, and patients who are not able to achieve and maintain optimal long-term disease control are in need of new treatment options.

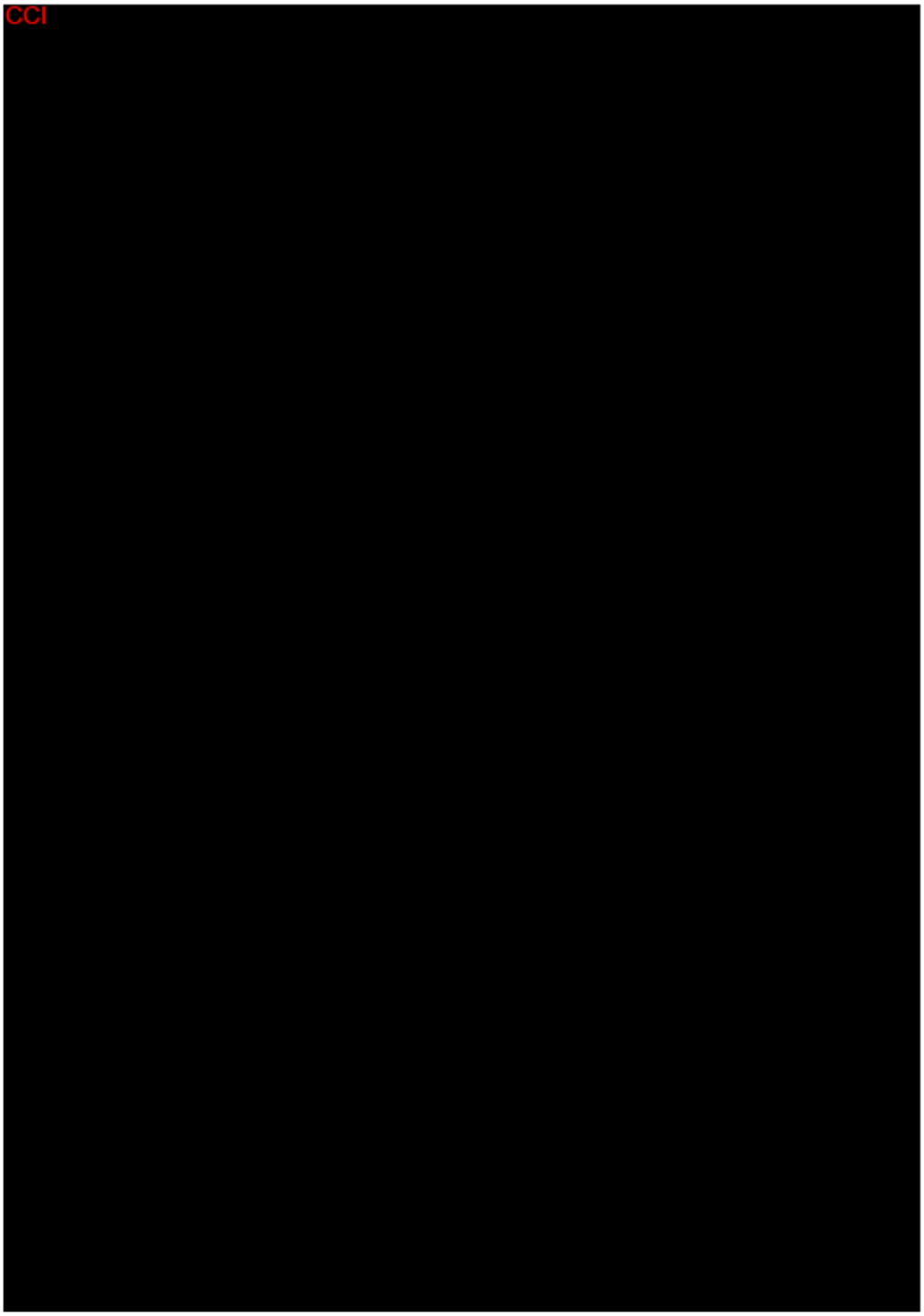
The current study aims to evaluate the efficacy and safety of lebrikizumab with concomitant TCS in patients with AD and a history of inadequate response or intolerance to CsA, or CsA-naïve patients for whom CsA treatment is not medically advisable.

5.1.2 Mechanism of Action

Lebrikizumab is a humanised monoclonal immunoglobulin (Ig) G4 antibody that binds specifically to soluble human IL-13 with high affinity and potently inhibits IL-13 signalling through the IL-4Rα/IL-13Rα1 complex, thereby preventing the downstream effects of IL-13 with high potency. Blockade of IL-13 signalling is expected to be of benefit in diseases in which IL-13 is a key contributor to the disease pathogenesis.

5.1.3 Nonclinical Studies

CCI



5.1.4 Clinical Studies

The safety and efficacy of lebrikizumab has been assessed in 3 completed clinical studies in patients with AD.

5.1.4.1 Efficacy

5.1.4.1.1 Study J2T-DM-KGAF/AD01

Study AD01 was a randomised, double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety of lebrikizumab monotherapy in adult patients (aged ≥18 years) with moderate-to-severe AD. The study consisted of a treatment period (16 weeks) and a follow-up period (16 weeks). Patients were randomised to 1 of 4 treatment groups (in a 3:3:3:2 ratio):

- lebrikizumab 125 mg every 4 weeks (Q4W) (with a loading dose of 250 mg)
- lebrikizumab 250 mg Q4W (with a loading dose of 500 mg)
- lebrikizumab 250 mg Q2W (with a loading dose of 500 mg on Day 1 and Week 2), or
- placebo Q2W.

The study treatment was administered subcutaneously. Patients discontinued use of TCS at least 7 days before enrolment and used an emollient twice daily during the 7 days before study start as well as throughout study participation. The primary endpoint was the percent change in the Eczema Area and Severity Index (EASI) score at Week 16. Key secondary endpoints were the proportion of patients at Week 16 who:

- had an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and a ≥2-point reduction
- had a ≥4-point change on the pruritus numerical rating scale (NRS)
- achieved a 90% reduction from Baseline in the EASI score (EASI 90)
- achieved a 75% reduction from Baseline in the EASI score (EASI 75), and
- achieved a 50% reduction from Baseline in the EASI score (EASI 50).

Key efficacy results were as follows:

- All 3 lebrikizumab groups showed statistically significantly greater reductions from Baseline in EASI score at Week 16 (primary endpoint) than the placebo group, indicating greater improvement in the extent/severity of AD with lebrikizumab than with placebo.
- The responses for the primary and secondary endpoint measures showed greater improvement with increasing dose.
- Statistically significantly greater proportions of patients in each of the lebrikizumab 250 mg Q4W and 250 mg Q2W groups achieved EASI 50, EASI 75, or EASI 90 at Week 16 than the placebo group.
- A statistically significantly greater proportion of patients in each of the lebrikizumab 250 mg Q4W and 250 mg Q2W groups had both an IGA score of 0 or 1 and a ≥2-point improvement in IGA score at Week 16 than the placebo group.

- While all 3 lebrikizumab groups showed statistically significant reductions from Baseline in pruritus NRS at Week 16 compared with the placebo group, only the lebrikizumab 250 mg Q2W group had a statistically significantly greater proportion of patients who achieved a ≥4-point improvement in pruritus NRS compared with the placebo group.
- Positive changes in pruritus led to positive changes in sleep; the lebrikizumab 250 mg Q4W and 250 mg Q2W groups had statistically significant percent reductions in sleep loss because of itching (as measured on a scale of 0 [no sleep loss] to 4 [unable to sleep at all]) compared with placebo (p=0.0459 and p=0.0062, respectively).

5.1.4.1.2 Study KGAG/GS29250 (TREBLE)

Study KGAG/TREBLE was a global, randomised, double-blind placebo-controlled study designed to evaluate the efficacy and safety of lebrikizumab in adult patients (aged 18 to 75 years) with persistent moderate-to-severe AD, who were inadequately controlled by TCS. In this study, lebrikizumab was evaluated as an add-on to TCS after 2 weeks of TCS run-in therapy and as single doses of 125 mg and 250 mg. CCI [redacted]

5.1.4.1.3 Study KGAH/GS29735 (ARBAN)

Study KGAH/ARBAN was a phase 2, randomised, open-label study. The primary objective was to evaluate the safety of lebrikizumab monotherapy in adult patients (aged 18 to 75 years) with persistent moderate-to-severe AD, who were inadequately controlled by TCS. This study included a 2-week TCS run-in period. Although the primary objective of the study was related to safety, the ARBAN study provided estimates of the treatment effect for lebrikizumab as monotherapy compared with triamcinolone 0.1% over a period of 12 weeks as part of an CCI [redacted] efficacy analysis. Twelve weeks of lebrikizumab 125 mg Q4W administered as monotherapy demonstrated improvements in AD. CCI [redacted]

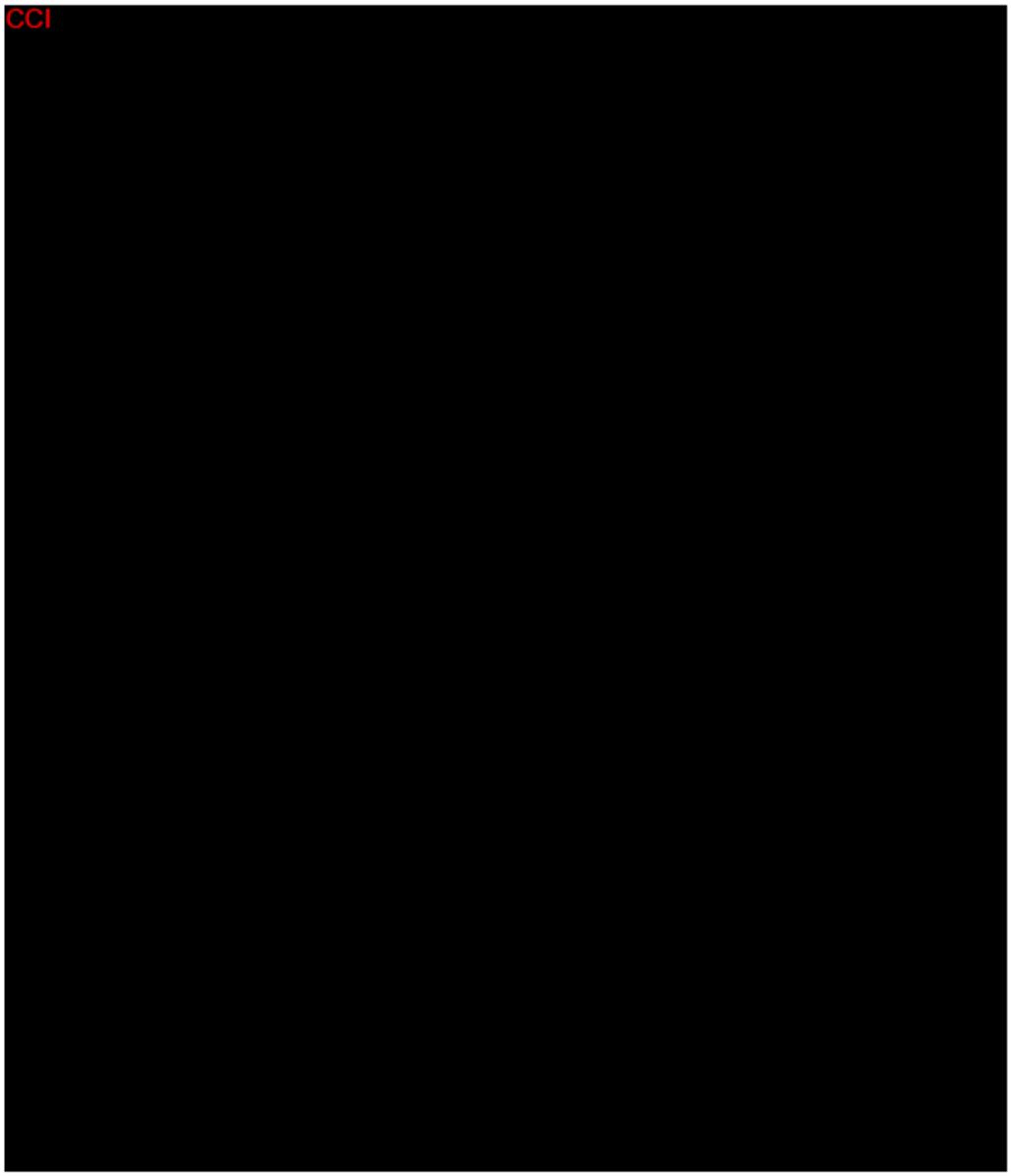
5.1.4.1.4 Phase 3 Programme

Currently a phase 3 programme of lebrikizumab in adults and adolescents with moderate-to-severe AD is ongoing to determine the safety and efficacy of lebrikizumab as monotherapy or in combination with TCS. The dose and dosing schedules being investigated in the phase 3

programme include 250 mg lebrikizumab Q2W for induction and either 250 mg lebrikizumab Q2W or 250 mg lebrikizumab Q4W as maintenance treatment. A loading dose of 500 mg lebrikizumab at first and second dosing is also being used. A total of 929 adult patients and 255 adolescent patients have been enrolled in the phase 3 studies to date.

5.1.4.2 Safety

CCI



5.2 Summary of the Known Potential Risks and Benefits

Treatment options are limited for patients with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications. Results of previous clinical studies have demonstrated a clinically significant effect of lebrikizumab on signs and symptoms of AD. On the basis of on cumulative safety data, the safety profile of lebrikizumab in the ongoing phase 3 programme has been shown to comprise largely predictable AEs that are mainly non-serious and is consistent with the safety profile reported in the phase 2 studies. Refer to Section 5.1.4.2 for details on the currently available information about the potential risks of lebrikizumab.

In this study, lebrikizumab will be administered in addition to standard therapy with TCS; therefore, patients who are randomised into the placebo arm will receive standard of care therapy and will be switched to lebrikizumab treatment after the initial 16 weeks of treatment. Additionally, TCS dosing can be adjusted to the patient's condition at the Investigator's discretion to prevent or treat flares. Patients who may be at higher risk of complications, such as those with a recent history of severe or recurring infections (in particular endoparasitic infection), immunosuppression, or positive viral serology results, will not be allowed to enter the study.

Further information regarding the preclinical and clinical characteristics, summary of the known potential risks and benefits, as well as reasonably expected AEs of the product under investigation are well described in the IB.

5.3 Scientific Rationale for the Trial

The use of lebrikizumab for AD is supported by numerous preclinical studies demonstrating that AD is characterised by the increased expression of IL-13 in skin. Moreover, 3 clinical trials (summarised in Section 5.1.4) with lebrikizumab demonstrated significant clinical benefit in patients with AD.

This trial is part of a phase 3 programme of lebrikizumab in adults and adolescents with moderate-to-severe AD. Cyclosporine is currently approved in the EU for treatment of severe AD. This trial aims to assess the response to lebrikizumab treatment in patients who have failed prior treatment with cyclosporine or who have medical contraindications to receive such treatment.

Additional detailed discussion of the lebrikizumab studies is provided in the lebrikizumab IB.

6 Objectives and Endpoints

Table 2 and Table 3 outline the objectives and corresponding endpoints that are to be assessed in the trial.

Table 2. Main Objectives and Related Endpoints

Main Objective	Endpoints
To evaluate the efficacy of lebrikizumab compared with placebo in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 16	**Primary Endpoint**: Percentage of patients achieving EASI 75 (≥75% reduction from Baseline in EASI score) at Week 16.

	Secondary Endpoints: • Percentage of patients achieving IGA 0/1 and 2-point improvement at Week 16.[a] • Percentage of patients achieving a 4-point improvement Pruritus NRS at Week 16.[a] • Percentage of patients achieving EASI 90 at Week 16. • Percentage of patients achieving EASI 75, EASI 90 and EASI 50 (by visit up to Week 16) • Change from Baseline BSA by visit up to Week 16 • Change from Baseline SCORAD by visit up to Week 16 • Change from Baseline Pruritus NRS by visit up to Week 16 • Change from Baseline sleep loss by visit up to Week 16 • Change from Baseline POEM by visit up to Week 16 • Change from Baseline DLQI/CDLQI by visit up to Week 16 • Percentage of patients achieving a 4-point improvement DLQI/CDLQI by visit up to Week 16 • Proportion of TCS-free days from Baseline by visit up to Week 16 • Time to TCS-free use (days) up to Week 16 • Change from Baseline Skin Pain NRS by visit up to Week 16 • Percentage of patients achieving a 4-point improvement Skin Pain NRS at Week 16. **Exploratory Endpoints:** CCI [redacted]

Abbreviations: BSA = body surface area; CDLQI = Children Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; DLQI-R = Dermatology Life Quality Index-Relevant; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; RECAP = recap of atopic eczema; SCORAD = Severity Scoring of Atopic Dermatitis; TCS = topical corticosteroids; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9 items; WHO-5 = World Health Organisation-Five Well-Being Index.

[a]relates to key secondary endpoints. While the sample size is aligned with the primary endpoint, these endpoints are also of interest in the final outcomes of the study. The sample size is appropriately aligned with the primary and key secondary endpoints.

Table 3. Secondary Objectives and Related Endpoints

Secondary Objectives	Endpoints
To evaluate the efficacy in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable between Week 16 up to Week 52.	• Percentage of patients achieving EASI 75, EASI 90, EASI 50 (by visit, between Week 16 and Week 52) • Percentage of patients achieving IGA 0/1 and 2-point improvement (by visit, between Week 16 and Week 52). • Percentage of patients achieving a 4-point improvement Pruritus NRS (by visit, between Week 16 and Week 52). • Change from Baseline BSA (by visit, between Week 16 and Week 52). • Change from Baseline SCORAD (by visit, between Week 16 and Week 52). • Change from Baseline Pruritus NRS (by visit, between Week 16 and Week 52). • Change from Baseline sleep loss (by visit, between Week 16 and Week 52). • Change from Baseline POEM (by visit, between Week 16 and Week 52). • Change from Baseline DLQI/CDLQI (by visit, between Week 16 and Week 52). • Percentage of patients achieving a 4-point improvement in DLQI/CDLQI (by visit, between Week 16 and Week 52). • Proportion of TCS-free days from Baseline (by visit, between Week 16 and Week 52) • Time to TCS-free use (days) • Change from Baseline Skin Pain NRS (by visit, between Week 16 and Week 52) • Percentage of patients achieving a 4-point improvement Skin Pain NRS (by visit, between Week 16 and Week 52). **Exploratory Endpoints:** CCI [redacted]

	CCI [redacted]
	Safety and Tolerability Endpoints
To evaluate the safety and tolerability of lebrikizumab in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 16	Incidence of AEs up to and including Week 16. AEs includes TEAEs, SAEs, Related TEAEs, Related SAEs, TEAEs leading to study treatment discontinuation, AESIs and Deaths.
	Observed results and changes from Baseline in Laboratory Results (Haematology, Chemistry and Urinalysis) to Week 16.
	Observed results and changes from Baseline in Vital Signs Results to Weeks 2, 4, 8, 12 and 16.
	Percentage of patients with abnormalities in physical examination at Week 16.
To evaluate the safety and tolerability of lebrikizumab in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 68	Incidence of AEs up to and including Week 68. AEs includes TEAEs, SAEs, Related TEAEs, Related SAEs, TEAEs leading to study treatment discontinuation, AESIs and Deaths.
	Observed results and changes from Baseline in Laboratory Results (Haematology, Chemistry and Urinalysis) to Weeks 32 and 52.
	Observed results and changes from Baseline in Vital Signs Results to Weeks 20, 24, 28, 32,36, 40, 44, 48 and 52.
	Percentage of patients with abnormalities in physical examination at Weeks 32 and 52.
Exploratory Objectives	**Other Endpoints**
CCI [redacted]	

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BSA = body surface area; CDLQI = Children Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; DLQI-R = Dermatology Life Quality Index-Relevant; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; NRS = numerical rating scale; POEM = Patient-Oriented Eczema Measure; RECAP = recap of atopic eczema; SAE = serious adverse event; SCORAD = Severity Scoring of Atopic Dermatitis; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9 items; WHO-5 = World Health Organisation-Five Well-Being Index.

7 Trial Design and Rationale

7.1 Trial Design

This is a randomised, double-blind, placebo-controlled, parallel-group study, 72 weeks in duration (up to 4 weeks of Screening, 52 weeks of treatment [last dose given at Week 50], and 18 weeks of post-last dose safety follow-up [SFU]). The study is designed to confirm the efficacy and safety of lebrikizumab administered concomitantly with TCS in adolescents and adults with moderate-to-severe AD not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable.

The study has 2 treatment periods: a 16-week double-blind Induction Period followed by a 36-week open-label Maintenance Period. The study will be double-blind until Week 18 and open-label from Week 20 onward. The patients who received placebo during the Induction Period will receive loading doses of lebrikizumab at Weeks 16 and 18. To maintain blinding at Weeks 16 and 18, all patients will receive 2 injections at Weeks 16 and 18 (either 2 injections of lebrikizumab or 1 injection of lebrikizumab and 1 injection of placebo) (

Table 4). From Week 20 onward, all patients will receive 1 injection of lebrikizumab 250 mg Q2W.

Study results will be delivered in 2 parts: the first results delivery will be provided after the first database lock, once all patients have completed the Induction Period or discontinued study before this point, and the second results delivery will be provided after second database lock, at the end of the study (EOS), once all patients have completed the study, or discontinued before EOS.

Accordingly, 2 different database locks will be used, and 2 different CSRs will be generated; one to cover the Induction Period, and the other to cover all data up to EOS. The first analysis will report the Induction Period only, and the second analysis will report all data up to EOS.

Eligible adult and adolescent (aged ≥12 to <18 years and weighing ≥40 kg) patients with moderate-to-severe AD for at least 1 year, defined according to the Hanifin and Rajka Criteria, [2] an EASI score of ≥16, an IGA score of ≥3 and a body surface area (BSA) affected by AD of ≥10% will be enrolled (adolescent patients aged ≥12 to <18 years will make up 12.5% of the overall population compared to adults aged ≥18 years). Eligible patients must have a documented history of inadequate response to treatment with topical AD medication within 6 months before Screening, documented history of inadequate response or intolerance to CsA, or CsA-naïve patients for whom CsA treatment is not medically advisable. Patients with previous exposure to dupilumab, including suboptimal responses (eg, persistence of itch despite treatment with dupilumab, flare-up days before the next dupilumab dose) may be included in the study with a washout period of 8 weeks before Baseline. During this washout period, patients may be allowed to use TCS, which will need to be stopped at least 1 week before Baseline. The enrolment of such subpopulation of patients will be limited to a maximum of 60 enrolled patients. All other enrolled patients must be naïve to IL-4 or IL-13 blocking antibodies.

The total duration of each patient's participation in the trial, including Screening, treatment, and follow-up periods, is estimated to be a maximum of 72 weeks (up to 4 weeks of Screening, 52 weeks of treatment [last dose given at Week 50], and a 18-weeks of post-last dose SFU).

After providing informed consent form (ICF)/informed assent form (IAF), patients will be assessed for study eligibility at the Screening visit. Patients will undergo Screening within 4 weeks before randomisation.

During the 16-week Induction Period, 312 patients will be randomised 2:1 to either 250 mg lebrikizumab (loading dose of 500 mg given at Baseline and Week 2) or placebo by SC injection Q2W. Randomisation will be stratified by previous use of dupilumab, age (adolescent patients aged ≥12 to <18 years will make up 12.5% of the overall population compared to adults aged ≥18 years) and baseline disease severity (IGA 3 versus 4). During the first 4 weeks of treatment as well as at Week 8, Week 12, Week 16, and Week 18 study drug injection will be administered in the clinic. Patients will have the option to self-administer study drug or get it administered by a caregiver outside the study site during weeks in which no on-site clinic visit is scheduled from Week 4 onward according to Table 1. Patients (and/or caregivers) will be trained on injecting study drug until competency has been demonstrated.

In case a patient is not willing to self-inject, their caregiver is not willing to do the injection, or the patient or caregiver does not demonstrate appropriate ability to do the injection, the clinic staff may administer all study drug injections throughout the study at the clinic.

All enrolled patients are required to start treatment with mid- or low-potency TCS at Baseline and continue it throughout the study as described in Section 9.9.2.

After completion of the Week 16 visit, patients will enter the Maintenance Period:

- Patients who received lebrikizumab 250 mg Q2W during the Induction Period will continue to receive lebrikizumab 250 mg Q2W during the Maintenance Period
- Patients who received placebo Q2W during the Induction Period will receive lebrikizumab 250 mg Q2W during the Maintenance Period

Patients who received placebo during the Induction Period will receive loading doses of lebrikizumab (500 mg) at Weeks 16 and 18 during the Maintenance Period.

To allow patients in the placebo arm to receive these lebrikizumab loading doses during the Maintenance Period, the blinding will be maintained at Week 16 and Week 18. Therefore, the study will be open-label from Week 20 onward, as summarised in

Table 4.

Table 4. Dosing Schedule During Maintenance Period

Randomised at Baseline to	Double-blind Dose at Week 16	Double-blind Dose at Week 18	Open-label Treatment After Week 20
250 mg lebrikizumab SC injection	1 injection of 250 mg lebrikizumab 1 injection of placebo	1 injection of 250 mg lebrikizumab 1 injection of placebo	1 injection of lebrikizumab 250 mg Q2W
Placebo SC injection	2 injections of 250 mg lebrikizumab	2 injections of 250 mg lebrikizumab	1 injection of lebrikizumab 250 mg Q2W

Abbreviations: Q2W = every 2 weeks; SC = subcutaneous.

Patients who do not achieve EASI 50 for at least 2 consecutive visits assessed at Weeks 24, 28, 32, 36, 40, 44, or 48 will be discontinued from the study.

Safety, laboratory, and clinical assessments will be performed as specified in the Schedule of Assessment (SoA) (Table 1).

Efficacy will be measured as follows:

- Clinical signs: EASI score, IGA score, BSA affected by AD lesions
- Clinical signs and patient reported symptoms: SCORAD score
- AD Patient Reported Symptoms: Pruritus NRS, Sleep-loss scale, Skin Pain NRS, Patient-Oriented Eczema Measure (POEM).
- Quality of life (QoL) and impact of disease: Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI), DLQI-Relevant (DLQI-R), World Health Organisation-Five Well-Being Index (WHO-5), Recap of Atopic Eczema (RECAP), and Treatment Satisfaction Questionnaire for Medication-9 items (TSQM-9).

Safety will be assessed by monitoring AEs, serum chemistry, haematology and urinalysis laboratory test results, physical examination results, and vital signs.

Blood samples will be collected at Baseline and Week 16 to assess biomarkers, CCI [redacted].

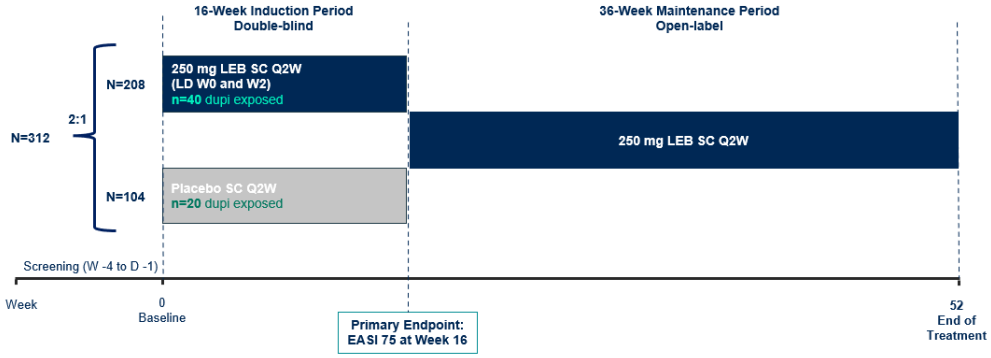
Photographs of lesions will be obtained from a subset of patients participating in this study as outlined in the Photography Manual. The photographs should not only include the lesion(s) but also a greater body area and the upper and lower body, including the face, limbs, and hands (back and palms).

Patients completing the study treatment and patients who terminate early will undergo a SFU visit approximately 18 weeks after the last study drug injection. For patients who complete the study, the last dose of treatment will occur at Week 50. Therefore, the SFU visit will occur at Week 68.

The EOS is defined as the date of the last visit of the last patient in the study shown in the SoA (Table 1).

The trial design is represented schematically in Figure 1.

Figure 1 Lebrikizumab Phase 3 Study Design Schematic



Abbreviations: D = day; dupi = dupilumab; EASI = Eczema Area and Severity Index Score; LD = loading dose; LEB = lebrikizumab; Q2W = every 2 weeks, SC = subcutaneous; W = week.

7.2 Trial Rationale

7.2.1 Rationale for Trial Design

The design for the Induction and Maintenance Periods for this trial is similar to the design used in the other lebrikizumab phase 3 trials and is commonly used in AD trials.

This study will enrol adult and adolescent patients with moderate-to-severe AD whose AD is not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable and therefore for whom a systemic treatment such as lebrikizumab may therefore be appropriate.

The Induction Period of the study has a double-blind, placebo-controlled design to guarantee an unbiased assessment of the primary and secondary efficacy variables at Week 16 in comparison with placebo. A duration of 16 weeks of placebo treatment is deemed acceptable in this patient population, also considering that all patients will receive background TCS therapy at a dosage that can be adapted based on the patient's needs.

Starting from Week 16, all patients will receive the active drug. From Week 20 onward, the study will have an open-label design to give patients randomised to placebo the opportunity to receive lebrikizumab treatment and to assess long-term efficacy and safety of lebrikizumab while adapting or discontinuing concomitant TCS therapy. Discontinuing patients who do not achieve or maintain a clinical response during the Maintenance Period will ensure that patients are not unnecessarily given treatment that is not effective.

TCS are the first-line anti-inflammatory treatment, even for patients treated with systemic therapies. For this reason, this study will assess the efficacy of lebrikizumab in combination with background mid or low-potency TCS, forced at Baseline and during the Induction Period, and used as determined appropriate by the Investigator from Week 16 onward.

7.2.2 Rationale for Trial Population

In this phase 3 study, adolescent patients (aged ≥12 to <18 years weighing ≥40 kg) will be included and will receive the same doses of lebrikizumab described above for adults (adolescent patients aged ≥12 to <18 years will make up 12.5% of the overall population compared to adults aged ≥18 years). The justification for this approach is as follows:

Both adults and adolescent patients have similar disease characteristics, typified by prominent type 2 skin inflammation and similar clinical manifestations. In addition, both groups tend to have similar efficacy outcomes in response to therapies, including dupilumab[39,40]. Pharmacokinetic (PK) modelling and simulations of lebrikizumab dosing (population PK modelling of pooled data from 2259 adult patients with asthma and a subsequent external posterior predictive check with lebrikizumab PK data from the DRM06-AD01 trial in adult patients with AD) revealed similar kinetics for adults and adolescent patients, aged 12 to <18 years. The maximal exposures are predicted to be slightly (≤35%) higher in adolescent patients than in adults for any given dose because of the lower adolescent weight ranges and lebrikizumab exposure dependence on weight; however, the safety profile in adolescent patients, based on the exposure-response relationship analysis and on partial extrapolation, is comparable to that observed in adults.

A subpopulation of patients previously exposed to dupilumab will be enrolled in the study with a maximum of 60 patients randomised. Patients may have discontinued dupilumab for any of the following reasons:

- lack or loss of efficacy or suboptimal response (ie, persistence of itch despite treatment with dupilumab, flare-up days before the next dupilumab dose)
- side effects or any other safety reasons
- end of participation in a dupilumab clinical trial
- end of reimbursement for dupilumab by National Health Services or health insurances
- personal decision

The enrolment of patients with prior exposure to dupilumab will serve to explore the extent and duration of response to lebrikizumab treatment in this subpopulation of patients within a randomised, placebo-controlled trial.

7.2.3 Rationale for Trial Dose and Regimen

The dosing regimen of a 500 mg loading dose at Baseline and Week 2, followed by 250 mg of lebrikizumab Q2W was selected for the lebrikizumab phase 3 programme based on an evaluation of safety, efficacy, and PK data from the clinical trials (see Section 5.1.4).

For the Maintenance Period, all patients will receive lebrikizumab 250 mg Q2W, because of the limited ability to collect insights that would reflect clinical practice and limited current understanding of which patients can benefit from Q4W dosing. Dosing flexibility data will not be generated in this study.

Additionally, the DRM06-AD03 PK study conducted in healthy adults demonstrated that a single SC injection of 2-mL (250 mg) of lebrikizumab delivered comparable levels of lebrikizumab as did 2 SC injections of 1-mL (125 mg). This study simulated the conditions under which study drug will be administered in phase 3, further supporting the dose and treatment regimen for phase 3 trials, lebrikizumab 250 mg Q2W with loading doses of 500 mg given at Baseline and Week 2, and at Week 16 and Week 18 during the Maintenance Period for patients who received placebo during the Induction Period.

7.2.4 Rationale for Trial Assessments

The efficacy assessments conducted in this study include clinician's and patient's reported outcome that have been validated and extensively employed in patients with AD.[4,41] The majority of assessments discussed below are also being employed in the other phase 3 trials of lebrikizumab. The frequency of assessments is deemed adequate to properly monitor development and achievement of response in terms of efficacy measures and QoL changes during the Induction Period, and the maintenance of a stable response over the Maintenance Period.

EASI, BSA, and IGA scores allow for evaluation of disease severity and extent as well as the physician's overall judgment at Screening and after study treatment. Achievement of EASI 75 response or IGA assessment of 0 or 1 are both response criteria used as primary or key secondary end points to confirm success of treatment in AD clinical trials. The SCORAD is a validated composite measure developed by the European Task Force of Atopic Dermatitis (ETFAD) that incorporates both objective physician's and subjective patient's assessments. POEM is a validated measure that uses patient-reported outcomes (PROs) specifically designed to measure AD severity from the patient's perspective.[38]

All pruritus entries will be recorded daily in the patient's diary from Week 0 to Week 2, weekly from Week 2 to Week 16 of the Induction Period, and every 2 weeks during the Maintenance Period.

All skin pain and sleep loss entries will be recorded daily in the patient's diary from Week 0 to Week 2, weekly from Week 2 to Week 16 of the Induction Period, and every 4 weeks during the Maintenance Period.

The RECAP is a newly designed patient questionnaire designed to capture AD control as experienced by the patient.[42]

QoL related to the patient's AD condition will be assessed by administration of the DLQI (adult or paediatric version [eg, the CDLQI] depending on the age of the patient), which is commonly used in AD clinical trials and often also in dermatology clinical practice.[43] The WHO-5 is a validated questionnaire measuring current positive mental well-being.[44] The scale has adequate validity both as a Screening tool for depression and as an outcome measure in clinical trials and has been widely used in clinical trials of any type of therapeutic indications. Depression has been associated with AD.[45]

The TSQM-9 is a reliable and valid instrument to assess patients' satisfaction with medication.[46]

Safety assessments including AEs, safety laboratory test results (haematology, chemistry, and urinalysis), vital signs, and physical examination findings will be performed at Screening visit to confirm eligibility criteria and at scheduled visits throughout the trial.

A predose blood sample will be collected at the Baseline visit for a biomarker analysis to characterise the enrolled patients with AD and explore any potential association with response to study treatment. Additionally, a predose blood sample will be collected at Week 16 to explore the potential biomarkers modification after treatment.

8 Selection of the Trial Population and Withdrawal of Patients

Study Investigators will review patient history and Screening test results at the Screening and Baseline visits to determine whether the patient meets all inclusion and none of the exclusion criteria to qualify for randomisation in the study. All Screening activities must be completed and reviewed before the patient is randomised

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

8.1 Number of Patients

A sufficient number of patients will be screened to randomise approximately 312 patients with moderate-to-severe AD.

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

8.2 Inclusion Criteria

Patients eligible for inclusion in this trial must fulfil all of the following criteria:

1. Adults and adolescents (aged ≥12 to <18 years at the time of ICF/IAF and weighing ≥40 kg)
2. Chronic AD (according to Hanifin and Rajka Criteria[2]) that has been present for ≥1 year before the Screening visit
3. EASI score ≥16 at the 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 Baseline visit
6. Documented history by a physician of an inadequate response to existing topical medications within 6 months before Screening, defined as: inability to achieve good disease control (eg, not able to achieve IGA ≤2) after use of at least a mid-potency TCS for at least 4 weeks, or for the maximum duration recommended by the product prescribing information (eg, 14 days for high/very-high-potency TCS), whichever is shorter
7. Documented history by a physician of either:
   a) No previous CsA exposure and not currently a candidate for CsA treatment because of
      i. medical contraindications (eg, uncontrolled hypertension on medication), or
      ii. use of prohibited concomitant medications (eg, statins, digoxin, macrolide antibiotics, barbiturates, anti-seizure drugs, nonsteroidal anti-inflammatory

drugs, diuretics, angiotensin-converting-enzyme inhibitors, St John's Wort, etc.), or

iii. increased susceptibility to CsA-induced renal damage (elevated creatinine) and/or liver damage (elevated function tests results), or

iv. increased risk of serious infections, or

v. hypersensitivity to CsA active substance or excipients

OR:

b) Previous exposure to CsA; CsA treatment should not be continued or restarted because of

i. intolerance and/or unacceptable toxicity (eg, elevated creatinine, elevated liver function test results, uncontrolled hypertension, paraesthesia, headache, nausea, hypertrichosis); or

ii. requirement for CsA at doses or durations beyond those specified in the prescribing information or inadequate response

8. Completed electronic diary (eDiary) entries for pruritus and sleep-loss for a minimum of 4 of 7 days before randomisation
9. Willing and able to comply with all clinic visits and study-related procedures and questionnaires
10. 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 18 weeks after the last dose of lebrikizumab or placebo
    - 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 patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception
11. Male patients must agree to use an effective barrier method of contraception during the study and for a minimum of 18 weeks following the last dose of study drug if sexually active with a WOCBP
12. Patient must provide signed ICF. Adolescent patients 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

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

1. Participation in a prior lebrikizumab clinical study

2. Treatment with IL-4 or IL-13 antagonists biological therapies before the Baseline visit. Exception: previous treatment with dupilumab will be allowed in a subset of patients (please see Section 7.2.2 for the definition of this subpopulation). A washout of at least 8 weeks before the Baseline visit will be required for this subpopulation
3. Treatment with TCS within 1 week before the Baseline visit
4. Treatment with topical calcineurin inhibitors, phosphodiesterase-4 inhibitors such as crisaborole, or cannabinoids within 2 week before the Baseline visit
5. Treatment with any of the following agents within 4 weeks before the Baseline visit:
    a. Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, interferon-γ, JAK inhibitors, azathioprine, methotrexate, etc.)
    b. Phototherapy and photochemotherapy (PUVA) for AD
6. Treatment with the following before the Baseline visit:
    a. An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer;
    b. B cell-depleting biologics, including but not limited to rituximab, within 6 months;
    c. Other biologics within 16 weeks or 5 half-lives (if known), whichever is longer
7. Treatment with a live (attenuated) vaccine within 12 weeks of the Baseline visit, planned during the study, or 18 weeks after the study treatment is discontinued
8. History of anaphylaxis as defined by the Sampson criteria[47]
9. Regular use (more than 2 visits per week) of a tanning booth/parlour within 4 weeks of the Screening visit
10. 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)
11. Have had any of the following types of infection within 3 months of Screening or develop any of these infections before randomisation:
    a. Serious (requiring hospitalisation, and/or IV or equivalent oral antibiotic treatment);
    b. Opportunistic (as defined in Winthrop et al. 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)
12. Have a current or chronic infection with hepatitis B virus
13. Have a current infection with hepatitis C virus (ie, positive for hepatitis C RNA)
14. Have known liver cirrhosis and/or chronic hepatitis of any aetiology
15. Diagnosed active endoparasitic infections or at high risk of these infections
16. 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 judgment

17. History of HIV infection or positive HIV serology at Screening
18. In the Investigator's opinion, any clinically significant laboratory test results from the chemistry, haematology, or urinalysis tests obtained at the Screening visit
19. Presence of skin comorbidities that may interfere with study assessments
20. 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
21. Severe concomitant illness(es) that in the Investigator's judgment would adversely affect the patient's 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 patient because of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments
22. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
23. Have had an important side effect to TCS (eg, intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects), as assessed by the Investigator or treating physician that would prevent further use

8.3.1 Patient Withdrawal

The Investigator will make reasonable efforts to keep each patient in the study. However, patients 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
- In the opinion of the Investigator, continued participation in the study is not in the best interest of the patient
- Serious protocol violation or procedure prohibited by the protocol
- Lost to follow-up

Before being withdrawn, patients will be requested to attend an end-of-treatment visit. All information, including the reason for being withdrawn will be recorded in the patient's study records and in the electronic case report form (eCRF).

A patient 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. 2 documented attempts (eg, telephone contact, emails) to contact the patient must be documented in a patient's study records for all patients who are believed to be lost to follow-up. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death.

8.3.2 Study Drug Discontinuation

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

- AE, laboratory abnormality or intercurrent illness for which continued treatment, in the opinion of the Investigator, would affect assessments of clinical status or patient safety to a significant degree
- TEAEs that are clinically significant, deemed persistent, and that, in the opinion of the Investigator, continued treatment would affect assessments of clinical status or patient safety to a significant degree
- Unacceptable toxicity
- Pregnancy
- Use of systemic rescue medication as outlined in Section 9.9.3
- No response to treatment as specified in Section 7.1

Patients who permanently discontinue study drug will be requested to:

- perform all the end-of-treatment visit assessments at their next scheduled site visit
- perform a SFU visit approximately 18 weeks after the last study drug injection, except for patients receiving systemic rescue medication as per Section 9.9.4.

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

8.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to trial intervention/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 observed. In case of a Screening laboratory value abnormality, the test can be repeated once within the original Screening time window, if the Investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

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.

8.4.1 Patient Replacement Criteria

Patients who withdraw from the trial at any time after randomisation will not be replaced.

8.5 Termination of the Trial

8.5.1 End of Trial Definition

The "end of trial" is defined as the date when all patients randomised in the trial complete follow-up contact (either Treatment Completers or those Prematurely Discontinued), or are lost to follow-up and have not been able to be contacted, and will be communicated to Competent Authorities and the independent ethics committee (IEC) in due time according to local regulations.

8.5.2 Completed Patient Definition

A patient attending the Week 16 visit will be considered a completer of the Induction Period.

A patient receiving the last study drug dose planned in the protocol will be considered a treatment completer, even in the absence of completing the SFU visit.

8.5.3 Premature Trial Termination

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

The entire study will be stopped if:

- Evidence has emerged that, in the collective opinion of the Investigators at each site with the concurrence of the Sponsor, or in the sole opinion of the Sponsor, continuation of the study is unnecessary or unethical
- The stated objectives of the study are achieved
- The Sponsor discontinues the development of the study for any reason (eg, lack of patient enrolment or non-compliance with clinical trial protocol, regulation, or good clinical practice [GCP] guidelines).

All data available for the patient at the time of study discontinuation must be recorded in the patient's records and the eCRF.

Certain additional 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
- The Sponsor considers the applied doses of the study drug to be no longer relevant.
- Data not known before becoming available that raise concern about the safety of the study drug so that continuation would pose potential risks to the patient

If the trial is terminated or suspended, the Sponsor will promptly inform the Investigators and the Competent Authorities. The Independent Ethics Committee (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).

Should the study be terminated, the decision and reason will be communicated in writing by the Sponsor to the Investigator with a request that all patients be discontinued. Patients should be scheduled for an end-of-treatment visit.

The Investigator will inform the patients 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 patient 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 implemented following good manufacturing practice (GMP) guidelines.

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 with a pre-assembled needle safety device (PFS-NSD)
Unit Dose/Strength	Each prefilled syringe is intended for a single 2 mL dose (250 mg)
Packaging Description	White folding carton with partition (167 × 54 × 40 mm)

Placebo Investigational Medicinal Product

Substance Code/Name	The placebo solution is identical in appearance and volume to the active solution except that it does not contain lebrikizumab
Route of Administration	Subcutaneous
Dosage Form	Solution for injection, containing the same excipients as the respective active lebrikizumab. Supplied as a sterile

	prefilled syringe with a pre-assembled needle safety device (PFS-NSD)
Unit Dose/Strength	Each prefilled syringe is intended for a single 2 mL dose
Packaging Description	White folding carton with partition (167 × 54 × 40 mm)

CCI

9.2 Packaging and Labelling

Packaging and labelling of IMP will be provided by the Sponsor and will comply with Annex 13 of the EU GMP regulations and local regulatory requirements.

Upon receipt of the study drug by the clinical research organisation (CRO), it will be inspected and counted by the responsible pharmacist. All study drugs will be labelled appropriately.

9.3 Shipment, Storage, and Accountability

Only participants enrolled in the trial (or parents/caregivers, if applicable) may receive the study drug and only authorised site staff may supply or administer the study drug. On-site, all drug supplies must be stored in a secure, environmentally controlled, monitored (manual or automated) area in accordance with the labelled storage conditions, with access limited to the Investigator and authorised site staff.

The Investigator, the trial staff, institution, or the head of the medical institution (where applicable) is responsible for clinical study drug or TCS 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 GCP guidelines, as well as local or regional requirements. Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Clinical study drug or TCS 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, unless the individual is the parent or caregiver of an adolescent participant.

Study drug is to be stored under refrigerated conditions (2°C to 8°C) and protected from excessive light and heat. Study drug should not be frozen, shaken or stored at room temperature. Temperature excursions outside of 2°C to 8°C must be reported to the Sponsor or the designee. Patients must report the date that the study drug is taken out of the refrigerator and the date of administration.

The Investigator 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 TCS must be stored according to leaflet instructions.

Used medication can be thrown away into special containers for injectable and medical waste, and empty boxes have to be stored for final accountability. If injection is done at home by the patient or their caregiver, the used syringes must be returned to the site in their respective original containers. Site personnel will then verify patient home compliance and dispose of the used medication into special containers for injectable and medical waste. 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 outlined in the Investigator's Drug Manual and/or Pharmacy Manual.

9.4 Treatment Administration

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

During the 16-week Induction Period, patients will receive either 250 mg lebrikizumab (loading dose of 500 mg given at Baseline and Week 2) or placebo by SC injection Q2W. The study drug injection will be administered in the clinic during the first 4 weeks of treatment as well as at Weeks 8, 12, 16, and 18. Patients will have the option to self-administer the study drug or get it administered by a caregiver outside of the study site during weeks in which no on-site clinic visit is scheduled from Week 4 onward according to Table 1. Patients (and/or caregivers) will be trained on study drug storage requirements, and on injecting study drug until competency has been demonstrated. After completion of the Week 16 visit, patients will enter the Maintenance Period:

- Patients who received lebrikizumab 250 mg Q2W during the Induction Period will continue to receive lebrikizumab 250 mg Q2W during the Maintenance Period
- Patients who received placebo Q2W during the Induction Period will start receiving lebrikizumab 250 mg Q2W (with loading doses at Week 16 and Week 18) during the Maintenance Period

To allow patients in the placebo arm to receive these loading doses during the Maintenance Period, blinding will be maintained at Week 16 and Week 18. In order to maintain the double-blind, patients from the lebrikizumab 250 mg Q2W arm will be administered a second injection of blinded placebo during Week 16 and Week 18. From Week 20 onwards, all patients will receive 1 injection of lebrikizumab 250 mg Q2W. Therefore, the study will be open-label from Week 20 onward. Please see the Pharmacy Manual for details on SC injection site management.

9.5 Treatment Compliance

Study drug compliance will be assessed by counting returned used or unused prefilled syringes. A patient will be considered compliant with the dosing regimen if the patient 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.

Patients will be instructed to return all used and unused TCS medication (tubes) to the study site for accountability purposes. Information on the areas where TCS was administered as well as the type of TCS will also be collected. The Investigator must keep an accurate record of the number of tubes received, dispensed/used, and returned by patients. The Sponsor or designee will provide forms to facilitate inventory control. All accountability forms and treatment logs must be retained in the Investigator's permanent study file, and these records must be available for inspection at any time by the Sponsor, its designees, or by regulatory agencies.

The dosing logs for each patient 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 Patients to Treatment Groups

9.6.1 Patient Identification

To protect the patient's identity and data confidentiality, each patient will be identified in the trial with 1 unique patient unique identifier. At Screening, the interactive web response system (IWRS) will assign a unique patient identification number to the patient, known as the patient number. This number will be associated with the patient throughout the study. Every patient who signs an ICF/IAF must be entered into the IWRS, regardless of eligibility, to obtain a patient 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 patient, starting at 001.

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

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

9.6.2 Randomisation

Patients who meet all criteria for enrolment will be assigned a randomisation number through the IWRS, in accordance with the randomisation code generated by the authorised personnel at PPD Once a randomisation number is allocated to a patient, it may not be assigned to another patient even if the former discontinued the study.

Eligible patients will be enrolled and randomised 2:1 on Study Day 1 to either 250 mg lebrikizumab (loading dose of 500 mg given at Baseline and Week 2) or placebo by SC injection Q2W. Randomisation will be stratified by prior use of dupilumab, age (adolescent patients aged ≥12 to <18 years will make up 12.5% of the overall population compared to adults aged ≥18 years), and baseline disease severity (IGA 3 versus 4).

Randomisation data will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding of the allocated treatment of all trial patients after database lock. When the trial is completed and the data verified and locked, the randomisation codes will be made available for data analysis.

The Investigator or his/her delegate will contact the IWRS after confirming that the patient fulfils all the inclusion criteria and does not meet any of the exclusion criteria. The IWRS will assign a randomisation number to the patient, which will be used to link the patient to a treatment arm and will specify unique medication pack numbers for the first packages of trial treatment.

9.7 Blinding

The 16-week Induction Period is a double-blind treatment period. While the Maintenance Period is generally open-label, the Weeks 16 and 18 doses will remain blinded so as to allow for patients in the placebo arm to receive a blinded loading dose before receiving maintenance open-label lebrikizumab during the Maintenance Period (from Week 20 onward).

Active and placebo medication will be supplied in individual carton boxes containing 1 syringe each. Lebrikizumab syringes cannot be distinguished visually from placebo syringes, as they have an identical appearance and components, including the syringe, needle safety device, folding carton, and labels.

A medication numbering system will be used in labelling blinded study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. To maintain the blind, these lists will not be accessible to individuals involved in study conduct.

No study site personnel, patients, Sponsor personnel, or Sponsor designees will be unblinded to treatment assignment throughout the study unless unblinding is required. If an Investigator becomes unblinded to a given patient's study treatment, that patient will be discontinued from the study unless there are ethical reasons for that patient not to be discontinued; approval from the Sponsor's medical monitor must be obtained in such instances.

In the event that emergency unblinding is required for a given patient because of AEs or concerns for the patient's safety or well-being, the Investigator may break the randomisation code for the patient via the IWRS, by which system the unblinding will be captured. The Investigator is responsible for notifying the medical monitor and/or Sponsor of such an event as soon as possible. Further details are provided in Section 9.8 below.

The Sponsor, CRO/vendors involved in the clinical conduct of the trial, the Investigators, trial site personnel, and patients will be blinded to the treatment that is assigned to each patient.

9.8 Unblinding by the Investigator

Whenever the maintenance of the safety and well-being of the patient – as assessed by the Investigator, requires the knowledge of the information on the administered study drug, the Investigator shall break the blind. Also, in the case of an unintended pregnancy of a patient or the female partner of a patient participating in the trial, the Investigator could break the blind.

In case of any doubt, the Investigator should contact the Sponsor/Medical Monitor from PPD to evaluate whether the blind should be broken.

The Investigator will call/access the IWRS indicating the trial patient concerned. A confirmation form will be sent to the Investigator specifying the treatment assigned, which will

be retained in the Investigator's file. The Sponsor PPD Pharmacovigilance Unit must be immediately informed of any unblinding.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor before unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation, as applicable.

9.9 Pre-trial, Concomitant, and Post-trial Medications/Therapy

9.9.1 Pre-trial Medications

To ensure proper washout and review of prohibited medications, any prohibited treatment or treatment requiring a washout period (as outlined in Table 5, and Section 9.9.2) taken by patient before signing the ICF be recorded in the eCRF (in Previous and Concomitant Medication).

A complete concomitant AD therapy history and reason for discontinuation (if applicable) will be recorded in the eCRF.

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 during the entire experimental phase of the trial. See Section 8.3 and Table 5 for background therapies that are not permitted in this trial.

Table 5. Prior Treatment Exclusions

Drug Class	Washout Period
IL-4 or IL-13 antagonists	N/A (not allowed)[a]
TCS	1 weeks
Topical calcineurin inhibitors	2 weeks
Phosphodiesterase-4 inhibitors (eg, crisaborole)	2 weeks
Cannabinoids	2 weeks
Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, JAK inhibitors, azathioprine, methotrexate)	4 weeks
Phototherapy and photochemotherapy (PUVA)	4 weeks
Investigational drugs	8 weeks or 5 half-lives (if known), whichever is longer
B cell-depleting biologics, including but not limited to rituximab	6 months
Other biologics	16 weeks or 5 half-lives (if known), whichever is longer
Live (attenuated) vaccine	12 weeks

Abbreviations: IFN = interferon; IL = interleukin; JAK = Janus kinase; PUVA = psoralen and ultraviolet A; TCS = topical corticosteroids.
[a]Prior treatment with dupilumab will be allowed in a subset of patients. A washout of at least 8 weeks before the Baseline visit will be required for this subpopulation.

9.9.2 Concomitant Medications

All medications (including prescription and non-prescription drugs, vitamins, and dietary supplements) taken after the patient signs initial ICF but before enrolment will be recorded in the eCRF as taken during the Screening Period. Thereafter, all nonstudy medications taken during the patient's participation in the study must be recorded, including the dose and regimen, start and stop dates, and indication.

At the Investigator's discretion, nonmedical topical moisturizers may be prescribed for the proper care and treatment of the patient, and TCS are required concomitant medications; administration is summarised in Table 6.

Table 6. Instruction for Use of Concomitant Medication

Concomitant Medication	Instructions for Use
Non-medicated topical moisturizer	Applied a stable dose at least BID for ≥7 days before the Baseline visit.
TCS	All patients must use concomitant TCS.
	At Baseline (Week 0, Visit 2) and until Week 16, all eligible patients will apply mid-potency TCS and low-potency TCS.
	Medium-potency TCS should be applied at least once daily to affected areas until lesions are under control (clear or almost clear). Patients should then switch to low-potency TCS and treat previously affected areas OD for 7 days and then stop.
	Low-potency TCS may be used from the Baseline visit in place of mid-potency TCS on areas of thin skin (face, neck, folds, and genital areas) and areas with skin atrophy. If lesions reappear during the course of the study, the patients should resume the OD applications of mid-potency TCS or low-potency TCS as described above.
	For patients whose lesions persist or worsen despite the use of emollients and low- and/or mid-potency TCS and/or patients who require daily applications on large surfaces, topical rescue with high- or very high-potency TCS may be considered for topical rescue with high- or very high-potency TCS.
	On the days of study visits, topical therapy, including TCS, should not be applied before the patient has undergone all study procedures and clinical evaluations including adequate assessment of skin dryness.
	From Week 16 to Week 52, TCS use will be at Investigator discretion and considered normal practice rather than an intercurrent event.
Inhaled corticosteroids and bronchodilators	To control asthma.

Abbreviations: BID = twice daily; OD, once daily; TCS = topical corticosteroids.

The use of TCS is prohibited for at least 1 week before the Baseline visit. A mid-potency TCS, triamcinolone acetonide 0.1% cream, and a low-potency TCS, hydrocortisone 1% cream (for use on sensitive skin areas), will be provided by the Sponsor or clinical site during the Induction Period only. The use of concomitant medications for other medical conditions (eg, hypertension, diabetes, acute infections) is permitted during this study.

9.9.3 Prohibited Concomitant Medications

The introduction of medications or therapies for other medical conditions known to have an effect on AD are not permitted during the study. These may include but are not limited to the list of medication as outlined in Table 5 and below:

- The use of systemic corticosteroids for the treatment of AD is prohibited and requires permanent discontinuation of the Investigational Product. If a systemic corticosteroid is used for the treatment of AEs (eg, worsening of existing condition, such as asthma exacerbation), it will be treated as rescue medication.

- Acute infections can be treated with systemic antibiotics, use of which must be recorded in the eCRF. However, chronic treatment with systemic antibiotics is not permitted.
- The use of a tanning booth/parlour is not permitted during the trial.
- Cannabinoid treatments for AD are prohibited.

9.9.4 Rescue Treatment for Atopic Dermatitis

If medically necessary (eg, to control intolerable AD symptoms), high-potency TCS or systemic treatments (eg, oral corticosteroids, phototherapy) may be used.

Patients using high-potency TCS will continue treatment with lebrikizumab and should continue to attend all study visits and be assessed for safety and efficacy according to the SoA.

Study drug must be permanently discontinued for patients receiving systemic rescue treatment as outlined in Section 9.9.3.

9.9.5 Post-trial Medications

Once the last dose of study drug is taken (eg, the last visit at which the patient takes IMP [Week 50]) and related trial measurements are completed (Week 52), patients should continue to take their usual medications, also allowed during the trial, and may resume other medications that were interrupted before trial enrolment as deemed appropriate by the Investigator.

The study drug is for experimental use only, and there are other therapies available to treat the disease.

Only concomitant medication associated with AEs will be captured between the last IMP administration and last phone contact/visit (between Week 50 and Week 68). From Week 52 onward, medications to treat AD will be recorded in the eCRF.

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. This can be done at any time before the Screening visit. ICF/IAF must be signed after the patient 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 patient´s medical records and a copy of the ICF/IAF will be given to the patient.

Trial visits will be scheduled in the morning whenever possible. 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 the randomisation visit day. To adapt appointments to local holidays, patient´s availability, or site internal organisation needs, a time window of ±3 days is allowed for visits during the Screening Period, Induction Period, and a time window of ±5 days is allowed for the SFU visit and visits during the Maintenance Period. PROs must be completed prior to other study-related activities. Therefore, the visit window for

PROs is -3 days during Induction Period and -5 days during Maintenance Period. Please contact the CRA or PPD 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 at the start of the visit before any other assessments or procedures. Assessments or procedures should be conducted in the following order: 1) PROs; 2) Investigator assessments and other efficacy assessments; 3) safety and laboratory assessments (including sample collection for biomarkers); and 4) administration of study drug.

Vital signs should be assessed before blood sampling.

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 patient (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.

An overview of the trial is provided in the SoA (Table 1), which summarises the trial procedures to be performed at each visit. Individual trial procedures are described below.

10.2 Patients General Conditions During the Trial

After the Screening evaluation and while not at the research site, patients will maintain normal daily activities, following the instructions of the Investigator. Patients 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 scheduled follow-up contact.
- Keep regular night/day shifts.
- Attend visits at which haematology/chemistry samples are to be collected under fasting conditions.
- Alcohol consumption will not be permitted for at least 8 hours before visits at which haematology/chemistry samples are to be collected.
- No use of hard drugs or other prohibited substances.
- Do not undergo hazardous physical activities beyond the patient's regular practice. Strenuous physical activity should be avoided for at least 8 hours before visits at which haematology/chemistry samples are to be collected.
- 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, including TCS, should not be applied before the patient 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 Patients

Male patients must agree to use an effective barrier method of contraception during the study and for a minimum of 18 weeks after the last dose of study drug if sexually active with a WOCBP.

10.3 Scheduled Activities and Trial Visits

10.3.1 Screening Period

The Screening Period will start with the Screening visit and continue until randomisation. The ICF/IAF must be signed before any trial-related procedures are performed.

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

Eligible patients 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

Patients 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. 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 the schedule detailed in Table 1.

10.3.2 Treatment Period

Treatment period visits and assessments will be performed in accordance with the SoA detailed in Table 1. See Sections 10.4 and Section 10.5 for details on the efficacy 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 in this protocol, in case of:

- technical problems with the equipment necessary for the visit
- any AEs that impede the conduct of the visit
- the intake of any prohibited medication, to reach the washout length required in the specific prohibited medication section of the protocol, as long as the delay fits the protocol-allowed time window.

10.3.3 End-of-Treatment

End-of-treatment visit and assessments will be performed in accordance with the SoA detailed in Table 1, after the last study drug administration (for completed patients) or premature discontinuation visit (when applicable).

10.3.4 Follow-up Period

A follow-up visit and assessments will be performed in accordance with the SoA detailed in Table 1, after the last study drug administration (for completed patients) or premature discontinuation visit (when applicable).

10.3.5 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 to follow-up with the progress of any clinically relevant abnormal finding, investigate any potential new AE, 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). The Investigator should repeat the individual test as soon as possible.
- At the Screening visit, any individual test(s) may be reasonably repeated before randomisation to confirm the eligibility criteria (eg, laboratory sample when there is any clinically significant abnormality).

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

10.4 Efficacy Assessments

Each patient's AD will be assessed as specified in the SoA (Table 1). Whenever possible, the same assessor should perform all assessments on a given patient during the course of the study. The Sponsor or delegate will administer training on the required efficacy 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 patient complete an assessment or questionnaire, they must not influence or question the response given by the adolescent patient 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.[48] 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 the patient's AD. It is based on a 5-point scale ranging from 0 (clear) to 4 (severe), 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 7. 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. BSA 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.[38] 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 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 patient (VAS only), as outlined in the SoA (Table 1).

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."[49] Assessments will be recorded by the patient using an eDiary, as outlined in the SoA (Table 1).

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

10.4.6 Sleep-Loss Scale

Sleep loss will be assessed by all patients using a PRO instrument. Patients (and if applicable, with help of parents/caregiver if required) will rate their sleep 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 patient using an eDiary, as outlined in the SoA (Table 1).

10.4.7 Skin Pain NRS

The Skin Pain NRS is a patient-administered, validated, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours."[50] Assessments will be recorded by the patient using an eDiary, as outlined in the SoA (Table 1).

The Baseline Skin Pain NRS will be determined based on the average daily Skin Pain NRS scores during the 7 days before Baseline. A minimum of 4 daily scores out of the 7 days before Baseline is required for this calculation.

10.4.8 Patient-Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire completed by the patient (and, if applicable, with help of parents/caregiver if required) to assess disease symptoms.[51] 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; 1-2 days = 1; 3-4 days = 2; 5-6 days = 3; every day = 4). A high score is indicative of a poor QoL. POEM responses will be captured using an eDiary, as outlined in the SoA (Table 1).

10.4.9 Dermatology Life Quality Index

The DLQI is a 10-item validated questionnaire completed by the patient or caregiver used to assess the impact of skin disease on the patient's QoL during the previous week.[52] 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. DLQI responses will be captured as outlined in the SoA (Table 1).

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.[53]

10.4.10 Dermatology Life Quality Index-Relevant

The DLQI-R is a recently developed scoring tool that adjusts the total score of the DLQI questionnaire for the number of not relevant responses indicated by a patient.[54-56]

10.4.11 World Health Organisation - Five Well-Being Index

The WHO-5 assessment is a self-reported measure of current mental well-being covering 5 positively worded items, related to positive mood (good spirits, relaxation), vitality (being active and waking up fresh and rested), and general interests (being interested in things).[44] Each item is rated on 6-point Likert scale, ranging from 0 (at no time) to 5 (all of the time). The raw scores are transformed to a score ranging from 0 to 100, with lower scores indicating worse well-being. WHO-5 responses will be captured from the patient as outlined in the SoA (Table 1).

10.4.12 Recap of Atopic Eczema

The RECAP is a 7-item patient-reported instrument to capture eczema control, over the previous week.[57] Each item is scored on a 5-point Likert scale, ranging from 0 (very good) to 4 (very bad). A higher score indicates worse eczema control. RECAP responses will be captured from the patient as outlined in the SoA (Table 1).

10.4.13 Treatment Satisfaction Questionnaire for Medication-9 Items (TSQM-9)

The TSQM-9 is a 9-item measure that assesses the most common dimensions patients use to evaluate their medication (ie, global satisfaction, effectiveness, and convenience).[46] The results for each scale are presented from 0 to 100, where higher scores represent better satisfaction. TSQM-9 responses will be captured from the patient as outlined in the SoA (Table 1).

10.5 Safety and Tolerability Assessments

10.5.1 Adverse Events

See Section 10.6 for AE definitions and reporting requirements.

10.5.2 Medical History, Physical Examinations, and Vital Signs

10.5.2.1 Medical History

A detailed medical history will be obtained by the Investigator or qualified designee at the Screening visit and recorded in the eCRF. The medical history will include immunisation records (for adolescent patients) and clinically relevant medical conditions or surgeries, including more specific information on a history of conjunctivitis and herpes infection/zoster. Information on the patient's AD (years since AD was diagnosed, anatomical areas affected by AD) and comorbidities (past history of asthma, allergic rhinitis/hay fever, conjunctivitis, food allergies, alopecia areata, prurigo nodularis, chronic hand eczema, herpes zoster [shingles], chickenpox [varicella-zoster], herpes simplex [eczema herpeticum, labialis (oral), genital], and eosinophilic esophagitis) will be collected and include the date of onset, extent of involvement, and past treatments for AD (and main reason for discontinuation) as well as comorbidities.

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

10.5.2.2 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. For this, patients should be in light indoor clothes without shoes. Specific head and neck lesions will be assessed at Baseline, Week 16, Week 32 and Week 52.

10.5.2.3 Vital Signs

Measurement of vital signs will include systolic and diastolic blood pressure (mmHg), pulse, respiratory rate (breaths per minute), and body temperature (°C). Measurements of systolic and diastolic blood pressure will be carried out after at least 5 minutes of resting in the supine position and always on the same arm. If there is any suspicion of an unreliable measurement, blood pressure will be measured again. The value obtained from the repeated measurement will be considered as definitive and should be recorded in the eCRF.

Significant findings that are observed after the patient has signed the ICF/IAF and that meet the definition of an AE must also be recorded in the eCRF.

10.5.3 Laboratory Testing

Blood and urine will be collected from each patient as specified in the SoA (Table 1) or as clinically indicated. Routine laboratory assessments will be analysed at a designated central laboratory (see Section 4.3). Tests to be performed are detailed in Table 8.

Table 8. 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 percentage of neutrophils, lymphocytes, monocytes, eosinophils and basophils), thrombocytes (platelet count)
Coagulation	At Screening only: Prothrombin time, activated partial thromboplastin time, and International Normalised Ratio
Blood chemistry	Electrolytes: Sodium, potassium, chloride, calcium, inorganic phosphate Enzymes: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and lactate dehydrogenase Substrates: Total cholesterol, triglycerides, urea, creatinine, total bilirubin, total protein, albumin, uric acid, and blood urea nitrogen
Serology	At Screening only: Hepatitis B surface antigen, Hepatitis B core antibody, Ig antibodies, anti-hepatitis C virus antibodies, and HIV I/II antibodies and antigen (serum)
Urinalysis	Dipstick measurements will be performed at the trial site* and will include: specific gravity, pH, blood, leucocytes, protein, glucose, bilirubin, urobilinogen, ketones and nitrites *If relevant abnormalities are detected (eg, > ++ positive result in dipstick), the urine sample will be sent to the central laboratory for analysis.
Pregnancy Testing	A serum beta-hCG test will be performed in all women of childbearing potential at Screening. All pre-menopausal women who are not sterile at Screening will also have a urine pregnancy test performed locally at all visits. Any woman with a confirmed positive pregnancy test during Screening is not eligible for randomisation. A positive urine pregnancy test during the treatment period of the trial requires a serum beta-hCG test to confirm the result.

Abbreviations: hCG = human chorionic gonadotropin; HIV = Human Immunodeficiency Virus; Ig = Immunoglobulin.

Blood and urine samples for laboratory testing will be collected in appropriate sampling tubes at scheduled time highlighted in the SoA (Table 1).

10.6 Adverse Events

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

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, or an abnormal finding in the physical examination.

AEs must be temporally associated with the patient's participation in the trial; ie, occur after the patients signs the ICF/IAF. 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 Events of Special Interest

The following TEAEs are being designated as Adverse Events of Special Interest (AESI):

- conjunctivitis
- herpes infection or zoster

The Investigator must report any AESIs within 48 hours from the moment she/he first learns of it to the Sponsor PPD pharmacovigilance unit. Additional data will be collected for AESIs during the treatment and follow-up phases. A specific follow-up form for conjunctivitis will be provided to the site. Patient records will include any follow-up information regarding these AESIs.

Serious Adverse Event

An SAE is an AE, that falls into 1 or more of the following categories:

- results in death
- is life-threatening (ie, an event that, in the view of the Investigator, places the patient 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 were more severe or had lasted longer
- requires in-patient hospitalisation or prolongs existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is any other medically important event that may jeopardise the patient or may require intervention to prevent one of the other above outcomes

Medical and scientific judgment should be exercised in deciding whether or not 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 jeopardise the patient 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."

Hospitalisation is defined as an overnight stay at the hospital or emergency room.

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

10.6.2 Reporting of Adverse Events

AEs either reported by the patient 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 patient). 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 intensity of the AE will be described in terms of mild, moderate or severe according to the Investigator's clinical judgment. And assign to 1 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 the use of the IMP will be described as:
  - **Not related**: Event or laboratory test result abnormality, definitely not related to study drug, or as related to another drug, chemical, or underlying disease.
  - **Unlikely related**: Event or laboratory test result abnormality, with a time relationship to study drug administration that makes a relationship improbable; disease or other drugs, chemicals or underlying disease provide plausible explanations.
  - **Possibly related**: Event or laboratory test result abnormality with a reasonable time relationship to study drug administration; 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 result abnormality with a reasonable time relationship to study drug administration, 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" 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, PPD 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 as:
  - Recovered/resolved
  - Recovering/resolving
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal
  - Unknown
- The action taken on the study drug will be captured as:

- Drug withdrawn
- 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 administration. In this latter case, the AE will be collected with each respective severity. The AE term recorded must be exactly the same in the different time points where AE is reported in the eCRF.

10.6.3 Recording of Adverse Events

AEs will be collected from the signature of the ICF/IAF up to 18 weeks after last study drug administration. Any AE reported by the patient from the last trial contact (follow-up telephone contact or visit) until Week 68, should be collected in the eCRF.

Medical disorders present at the time the patient signs the ICF/IAF that are part of the patient's medical history will only be considered AEs if they worsen after this time.

Abnormalities detected before IMP administration during physical examination, laboratory tests, 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 or case report form medical history/physical examination form/page. However, abnormalities detected in Screening/Baseline tests that are not part of the patient's medical history will be considered AEs.

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

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

AEs will be elicited by asking the patients non-leading questions (eg, "How do/did you feel?) and by collecting AEs spontaneously, as reported by the patient to the Investigator or 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, it is 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 collected from signature of ICF/IAF up to 18 weeks after last study drug administration.

The Investigator must report any SAE within 24 hours from the moment she/he first learns of it to the Sponsor/PPD 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 patient.

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

The trial centre must transmit the SAE report form and pregnancy form to the following SAE email or fax number: **drug.safety.services@almirall.com or +34 93 291 2829**

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 patient, defined as a patient who has consented to participate in this trial
- A suspect medicinal product
- 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 process will be continued until the event has been fully documented and reported.

An event reported to the Sponsor PPD pharmacovigilance unit that 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 PPD pharmacovigilance unit and submitted to the Competent Authorities, IEC, and/or Investigators, when applicable according to local regulations.

SAEs NOT considered reportable to the Sponsor will be:

- Hospitalisation for a treatment/surgical procedure that was elective or pre-planned for a pre-existing condition that did not worsen during the participation in the trial
- Events that result in hospital stays for observation of <24 hours and that do not require a therapeutic intervention/treatment (eg, an emergency room visit for haematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics)

10.6.5 Suspected Unexpected Serious Adverse Reactions

AEs 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 safety information)
- 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 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

All AEs/SAEs that are still present after the last study drug administration (including AEs that have led to premature discontinuation), will be followed-up for at least 2 weeks after the last study drug administration for AEs and 4 weeks after the last study drug administration for SAEs, unless otherwise specified in the protocol, by means of a follow-up contact or visit (whichever is considered more appropriate by the Investigator). SAEs and non-serious AEs of special interest, will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up. AEs still ongoing after that time point, will be evaluated by the Investigator and treated and followed until the symptom(s) return to normal or to clinically acceptable levels, as judged by the Investigator. The same timeframes will apply for AEs from Screening failures that are ongoing at the time the patient 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 in the clinical database, if this was already locked; therefore, the clinical database lock will not be delayed because of 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

If an overdose (defined as any dose higher than doses described in this protocol) 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 patient 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 patients to inform them immediately if they become pregnant during the trial and up to 18 weeks after last IMP dose.

In case of pregnancy during the participation in the trial, the patient will be immediately considered for premature discontinuation.

All pregnancies beginning during the patient's participation in the trial or up to 18 weeks after last IMP administration, which come to the knowledge of the Investigator, after the clinical trial termination will be reported to the Sponsor PPD pharmacovigilance unit as throughout the trial.

The Investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it to the Sponsor PPD pharmacovigilance unit within 24 hours of confirmation of the pregnancy. Pregnancy is not itself an AE or SAE; however, maternal/fetal 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 new-born 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, fetal death, SAE in a neonate and congenital abnormalities will be reported as SAEs. The Investigator will inform the Sponsor PPD 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 18 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 18 weeks after last IMP dose.

10.6.9 Unblinding for Safety Reasons

For any unblinding done by Investigator, please refer to Section 9.8.

According to pharmacovigilance legislation the Sponsor's Corporate Drug Safety Department can break the blind of specific patient for regulatory reporting purposes (ie, suspected unexpected serious adverse reaction [SUSAR] case). Unblinding will be done according to the applicable SOP.

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 adverse event 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

CCI

CCI

[redacted]

10.7.2 Photography

Photographs of lesions will be obtained from a subset of patients participating in this study as outlined in the Photography Manual. The photographs should not only include the lesion(s) but also a greater body area, upper and lower body including face, limbs and hands (back and palms).

11 Statistics

11.1 Sample Size Calculation

The study is designed to gain an estimate of the effect of study treatment in the patient population of adults and adolescent patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable. The sample size for this study has been estimated to allow power enough to show efficacy in the overall study population for the primary and key secondary endpoints.

In the overall population, a total sample size of 312 patients, in a 2:1 ratio (208 lebrikizumab arm and 104 placebo arm) will provide more than 95% nominal power to detect a statistically significant difference of 25% (55% lebrikizumab arm versus 30% placebo arm) in the primary study endpoint: proportion of patients achieving EASI 75 at Week 16. As reference and considering independence between variables, this same sample size will provide more than 90% overall power to also detect a difference of 18% (30% lebrikizumab arm versus 12% placebo arm) in the proportion of patients achieving IGA (0/1) at Week 16 and of 34% differences (43% lebrikizumab arm versus 9% placebo arm) in the proportion of patients achieving a 4-point pruritus NRS decrease from Baseline at Week 16.

11.2 Structure and Methodology of the Statistical Analysis

Statistical analyses of demographic, baseline characteristics, efficacy, and safety and tolerability data will be performed by PPD Biostatistics department. A fully specified SAP will be prepared by PPD statistician under the Sponsor's SOPs before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

SAS version 9.4 or greater (SAS Institute, Cary, NC) will be the statistical software used to analyse the data sets. A complete set of patient data listings will be appended to the statistical report. All tables, figures, and listings will be presented in PDF format without any manual editing, ie, they will appear unmodified as programmed by means of the statistical package.

Tables, figures, and listings will be compiled in the statistical report and appended to the CSR. As stated previously, for the study there will be 2 CSRs, one reporting the Induction Period results and one reporting all data up to the EOS. For this reason, analyses of these periods will be presented separately, except for time-to-event analyses at EOS. For the Induction Period analysis, the treatment groups as randomised/received at Baseline will be presented; for the Maintenance Period, the treatment as received from Week 20 onward will be presented.

All endpoints described in Section 6 will also be analysed by previous exposure to dupilumab (Yes/No) as CCI

11.3 Analysis Populations

The following analysis sets are defined:

- The Full Analysis Set (FAS) includes all randomised patients. Patients will be analysed under the treatment group as randomised.
- The Per Protocol Analysis Set (PPS) includes all randomised patients who receive at least one dose of the study drug, have at least one post-Baseline EASI assessment, and additionally for whom there are no important protocol deviations affecting efficacy at Week 16. Patients will be analysed under the treatment group as randomised.
- The Safety Analysis Set (SAF) includes all randomised patients who receive at least 1 dose of the study drug. Patients will be analysed under the treatment group actually received.

The precise reasons for excluding patients from the PPS population, and other pre-defined data handling issues will be fully defined and documented in the corresponding Blind Data Review Meeting (BDRM) reports, finalised before unblinding of the study.

The main analysis of all the efficacy variables will be performed on the FAS population. The primary and key secondary efficacy variables will also be analysed for the overall population using the PPS population to assess the robustness of the findings from the FAS population. All safety analyses will be conducted using the SAF population.

11.4 Descriptive Statistics

Summary statistics will be presented by study period and treatment group. The Induction and Maintenance Periods will be reported separately. Categorical variables will be summarised with counts (n) and percentages (%) and will be tabulated by treatment and/or overall where appropriate. For continuous variables, the number of non-missing observations (n), mean, standard deviation, standard error of the mean, median, first and third quartiles, minimum and maximum will be tabulated by treatment and/or overall. When applicable, these summaries will be provided by visit and time point of assessment. The 95% CI around the mean may also be presented in descriptive statistics as appropriate for specific endpoints of interest.

11.5 Patient Disposition

The number of patients included in each analysis set and the reasons for discontinuation will be summarised using descriptive statistics by study period and treatment group. In addition, patients' status with regard to study treatment within each study period and follow-up will also be summarised by study period and treatment group. Summaries of disposition will be based on all patients enrolled, regardless of randomisation.

11.6 Demographic and Baseline Characteristics

The trial population will be described using demographic and baseline characteristics recorded during before the first study drug administration. 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 used to summarise demographic and Baseline characteristics, including but not limited to sex, age, region, race, height, weight, body mass index (BMI), skin type (Fitzpatrick scale[3]) and prior use of dupilumab. For stratification factors, both the factor as randomised and the actual factor will be summarised, if differences exist. Medical history information will be presented in a by-patient listing. 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 for the full list of objectives and study endpoints. Descriptions of the estimands for the study are included in Section 11.8.1.1.

11.8 Statistical Methods

The statistical approach for the analysis of primary and secondary efficacy endpoints is described below. The full statistical methodology to be applied for primary and secondary endpoints, and additional endpoints will be detailed in the SAP.

As discussed in Section 7.1, study results will be delivered in 2 parts: the first results delivery will be provided after the first database lock, once all patients have completed the Induction Period or discontinued study before this point, and the second results delivery will be provided after second database lock, at the EOS, once all patients have completed the study, or discontinued before EOS. The first analysis will report the Induction Period only, and the second analysis will report all data up to EOS.

11.8.1 Analysis of Efficacy

The primary analyses for efficacy will be based on the FAS. Furthermore, the primary and key secondary efficacy variables will be also analysed for the overall population using the PPS population to assess the robustness of the findings from the FAS population. Refer to Section 11.3 for details of the specific analyses to be conducted under the PPS population. As CCI , all efficacy endpoints will be analysed as well by previous exposure to dupilumab (Yes/No).

11.8.1.1 Primary Efficacy Analysis (Overall Population)

A. Primary and Key Secondary Efficacy Endpoints

The primary efficacy analysis will be based on the main estimand for the overall population (FAS). The objectives, variables and population-level summary measures for the main estimand for the primary efficacy endpoint and key secondary endpoints is provided in Table 9.

Table 9. Main Estimand for Primary and Key Secondary Efficacy Analyses

Objectives/Treatment Condition of Interest	Variable/Outcome Assessed	Population-Level Summary Measure
To evaluate the efficacy of lebrikizumab compared with placebo in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 16 (ie, at the end of the Induction Period).	**Title:** EASI 75, IGA(0/1) and 2pt improvement, 4pt improvement in Pruritus NRS **Description:** Patient achieving: EASI 75: ≥75% reduction in EASI score from Baseline, IGA: IGA score of 0 or 1 with 2pt improvement from Baseline, Pruritus NRS: 4pt improvement from Baseline **Time Frame:** 16 weeks	**Population:** Adult and Adolescent Patients with Moderate-To-Severe AD that are not Adequately Controlled with Cyclosporine or for whom Cyclosporine is not Medically Advisable. **Measure:** Difference between treatments (lebrikizumab minus placebo) in proportion of subjects achieving EASI 75, IGA criteria, pruritus NRS criteria at Week 16

Abbreviations: AD = atopic dermatitis; EASI = Eczema Area and Severity Index (score).

Intercurrent Events (ICEs) for the Primary and Key Efficacy Endpoints:

The following ICEs are envisioned during the study, to be considered up to and including the Week 16 assessment:

a) ICE1: Patient prematurely discontinues study treatment due to reasons other than lack of efficacy prior to Week 16.

b) ICE2: Patient prematurely discontinues study treatment due to lack of efficacy prior to Week 16.

c) ICE3: Patient receives rescue medication prior to Week 16 (either allowed or prohibited) for treatment of AD, as per Section 9.9.

Further ICEs may be added as appropriate, for example to describe the effects of COVID on the response observed if applicable. The full list of ICEs will be detailed in the SAP.

For supportive analyses, a second estimand will be used.

The ICEs will be handled using the following approaches to be applied under the main and second estimands (Table 10):

Table 10. Handling of ICEs for the Primary Efficacy Endpoint and Key Secondary Endpoints (for the Main and Second Estimands)

Estimand	Analysis Strategy for ICEs		
	Treatment Discontinuation due to:		
	ICE1: Reasons Other than Lack of Efficacy	ICE2: Lack of Efficacy	ICE3: Rescue or Prohibited Meds for Treatment of AD
Main Estimand (Hybrid)	Hypothetical Strategy: Set to missing	Composite Strategy: Set to baseline	Composite Strategy: Set to baseline

Estimand	Analysis Strategy for ICEs		
	Treatment Discontinuation due to:		
	ICE1: Reasons Other than Lack of Efficacy	ICE2: Lack of Efficacy	ICE3: Rescue or Prohibited Meds for Treatment of AD
Second Estimand: Categorical Endpoints (Composite)	Composite Strategy: Set to non-responder	Composite Strategy: Set to non-responder	Composite Strategy: Set to non-responder

Abbreviations: AD = atopic dermatitis; ICE = intercurrent event.

Details on missing data imputation are described in Section 11.10.

- Main Estimand (Hybrid):
  - The approach for the main estimand is a hybrid estimand representing the primary clinical question of interest: what is the difference between treatment conditions, ie, Lebrikizumab vs Placebo, in the target patient population, in successful responses after 16 weeks achieved without use of rescue medication and if all patients continued with treatment except those who discontinued due to lack of efficacy?

- Second Estimand:
  - The second estimand for categorical endpoints is a composite estimand representing the supportive clinical question of interest: what is the difference between treatment conditions in the target patient population, in successful responses after 16 weeks achieved without use of rescue medication or treatment discontinuation?

The complementary estimand approach here allows for an estimate of the effects of the different events to be ascertained.

Statistical Hypotheses:

The statistical hypotheses to be tested for the main estimand are:

- H_0: $P_{Lebrikizumab} - P_{placebo} = 0$
- H_1: $P_{Lebrikizumab} - P_{placebo} \neq 0$,

where $P_{Lebrikizumab}$ refers to the proportion of patients receiving lebrikizumab, and $P_{placebo}$ refers to the proportion of patients receiving placebo that achieve EASI 75 at Week 16. The testing procedure will thus be 2-sided. Confirmatory testing is conducted using the main estimand.

Analysis Model:

The primary and key secondary endpoints (for the main and second estimands) will be analysed by means of a Cochran-Mantel-Haenszel (CMH) model adjusted by country, age (adolescents/adults), prior use of dupilumab (yes/no), and baseline severity of disease (IGA=3/IGA=4). The FAS will be the primary analysis set; if the model does not converge, country will be removed as an adjusting factor. The estimate of the adjusted common risk difference, with corresponding Mantel-Haenszel-Sato (Sato 1989)[58] adjusted 2-sided 95% CI and p-value will be presented. Additionally, the CMH adjusted odds ratio along with the 95% two-sided asymptotic CI will be presented.

For analyses using multiple imputation, the analysis will be conducted on the complete dataset, for each imputation separately. Modelled results will be combined using Rubin's rule (PROC MIANALYZE) for tabulation.

Sensitivity Analysis for the Primary and Key Secondary Efficacy Endpoints:

The following sensitivity analysis will also be conducted for the main and second estimands of the primary and key secondary efficacy endpoints, on the overall population:

Table 11. Sensitivity Analysis

Analysis Set	Modelling Method	Estimand and Data Handling
Sensitivity Analysis Conducted on Main and Second Estimands		
PPS	CMH model adjusted by country, and stratification factors used in the randomisation (age, previous use of dupilumab, and baseline severity of disease, as per primary analysis).	As per main and second estimands

Abbreviations: CMH = Cochran-Mantel-Haenszel; PPS = Per Protocol Set.

Additional subgroup analyses based on baseline characteristics will be presented as appropriate using forest plots.

All inferential analyses of the primary and key secondary efficacy endpoints, including multiple imputation approaches, will be conducted during the Induction Period only (eg, up to and including Week 16). During the Maintenance Period, only descriptive analyses will be performed for efficacy. The handling of estimands as detailed above will also only apply up to and including Week 16. After this point, data will only be analysed as observed.

B. All Other Secondary and Other Efficacy Endpoints

All binary other secondary and other efficacy endpoints will be analysed using the same methodology as described above for the primary efficacy endpoint using only the main estimand. Sensitivity analyses based on the PPS population will not be conducted for these endpoints.

Continuous other secondary endpoints assessed at multiple post-Baseline visits during the Induction Period will be analysed on the following estimands (Table 12):

Table 12. Handling of ICEs for the Continuous Secondary Efficacy and Other Efficacy Endpoints

Estimand	Analysis Strategy for ICEs		
	Treatment Discontinuation due to:		
	ICE1: Reasons Other than Lack of Efficacy	ICE2: Lack of Efficacy	ICE3: Rescue or Prohibited Meds for Treatment of AD
Main Estimand (Hybrid)	Hypothetical Strategy: Set to missing	Composite Strategy: Set to baseline	Composite Strategy: Set to baseline

Estimand	Analysis Strategy for ICEs		
	Treatment Discontinuation due to:		
	ICE1: Reasons Other than Lack of Efficacy	ICE2: Lack of Efficacy	ICE3: Rescue or Prohibited Meds for Treatment of AD
Second Estimand: Continuous Endpoints (Hypothetical)	Hypothetical Strategy: Set to missing	Hypothetical Strategy: Set to missing	Hypothetical Strategy: Set to missing

–Abbreviation: ICE = intercurrent event; AD = atopic dermatitis.

The main and second estimands will be analysed by means of a mixed effect model for repeated measures (MMRM) including the baseline value as a covariate, and adjusting by the factors of country, age (adolescents/adults), baseline severity of disease (IGA=3/IGA=4), previous exposure to dupilumab (yes/no, when the overall population is analysed), and visit and treatment-visit interaction. A restricted maximum likelihood method will be specified, along with an unstructured covariance matrix. Estimates of the LS Means for each of the 2 treatment groups at each visit up to and including Week 16, along with the difference between treatments in LS Means, 2-sided 95% CI, and p-value for the difference will be presented.

Missing data will be handled as per Table 13.

For all continuous secondary efficacy endpoints described above, in case of non-convergence, the country factor will be removed from the model.

Time-to-event (TTE) endpoints will be analysed on the second estimand for continuous endpoints using Kaplan-Meier survival analysis methods. If available, for descriptive purposes, the estimate of the median time-to-event (in weeks) and the 2-sided 95% CI will be presented. A comparison of the survival distribution curves for the 2 treatment groups will be made by means of the log-rank test. The Cox proportional hazards model will be used to estimate the hazard ratio and its 95% CI of lebrikizumab compared with placebo at the respective time point. The main Cox proportional hazards model will include treatment group, with country, age, baseline disease severity and previous exposure to dupilumab (when the overall population is analysed) as factors. The proportional hazard assumption will be evaluated on all factors (ie, treatment and stratification factors) by graphical inspection of the Schoenfeld residuals and by Grambsch and Therneau test as well. Country may be removed from the model as appropriate, similar to the other analyses of efficacy. Because of the fact that the Induction and Maintenance Periods will be reported separately, TTE endpoints will be analysed at 2 separate time points: initially up to and including Week 16, and then separately for the whole study, incorporating both the Induction and Maintenance Periods.

All efficacy variables for the Maintenance Period will be analysed by means of descriptive statistics presented by treatment group as randomised during the Induction Period.

11.8.1.2 Subgroup Efficacy Analyses (Dupilumab Naïve and Patients Previously Exposed to Dupilumab)

The same analyses described for the Primary efficacy analyses (Section 11.8.1.1) will be performed in each of the two subgroups described, for CCI purposes.

All efficacy variables for the Maintenance Period for subgroup analyses will be analysed by means of descriptive statistics presented by treatment group as randomised during the Induction

Period, in the same way as for the primary and secondary efficacy analyses on the overall population.

11.8.2 Analysis of Quality of Life Endpoints

The Quality of Life (QoL) endpoints of Total DLQI and CDLQI will be analysed in the same way as the continuous other secondary efficacy endpoints occurring at multiple post-Baseline visits on the overall population.

DLQI-R, RECAP, TSQM-9, and WHO-5 will all be analysed descriptively on the overall population. Any individual components related to QoL scoring will also be analysed descriptively for the overall population.

All QoL endpoints and related individual components will also be analysed descriptively for the Maintenance Period, presented by treatment group as randomised during the Induction Period.

11.8.3 Analyses of Endpoints Related to the Secondary Objective (From Week 16 to Week 52)

All variables described in Table 3 from Section 6 will be analysed by means of descriptive statistics overall and separately, considering the arm where they were randomized during the induction period. More detailed description will be provided in the SAP.

11.8.4 Analysis of Safety and Tolerability Endpoints

The analyses of safety and tolerability outcomes will be performed on the SAF. Safety outcomes include AEs, vital signs (including body temperature, respiratory rate, pulse, and systolic and diastolic blood pressure), physical examinations (including application site reactions), and clinical laboratory assessments (haematology, chemistry panel, urine testing, and urine pregnancy test for WOCBP).

Baseline will be defined as the latest value before IMP administration on Day 1 of the study. In case of missing predose values, the value at Screening will be regarded as the Baseline value. For the follow-up visit the comparisons will be performed against Screening values.

Safety variables:

- AEs will be summarised as an overall proportion of patients with at least one AE, proportion of patients with at least one SAE, proportion of patients with at least one severe AE, proportion of patients with at least one related AE, proportion of patients with at least one AE leading to treatment or study discontinuation. Each patient will contribute only once (eg, the first occurrence) to each of the rates, regardless of the number of occurrences (events) the subject experiences.
- Treatment-emergent AEs will be summarised and tabulated by System Organ Class and PT, by severity (mild, moderate, severe), by seriousness, by action taken with the study drug (continued, interrupted or discontinued), by outcome (Recovered/resolved, Recovering/resolving, Recovered/resolved with sequelae, Not recovered/not resolved, Fatal, unknown), by relationship to study product (not related, unlikely related, possibly related, and related), and for AEs of clinical interest.

- An AE will be considered a TEAE if it was not present before the first dose of study drug or was present before the first dose of study drug but increased in severity during the treatment period. Any event with a missing onset date will be included as a TEAE.
- Deaths and SAEs will be listed by subject.
- Clinical Laboratory Tests: Laboratory parameters will be summarised using descriptive statistics at Baseline and at each subsequent pre-defined time point by treatment group. In addition, shift tables (ie, low-normal-high at Baseline versus low-normal-high at follow-up in a 3-by-3 contingency table) will be provided to assess changes in laboratory values from Baseline to follow-up in each treatment group and overall.
- Other Safety Measures: Vital signs, physical examinations, local skin reactions, and, if applicable, AESIs, and pregnancy test results will be listed and summarised descriptively.

Descriptive statistics will be used to summarise study and treatment compliance.

Prior and concomitant medication information will be presented in a by-patient listing.

11.9 Analysis of Biomarkers

CCI

[redacted]

11.10 Handling of Missing Data

Every effort will be made to prevent patients withdrawing from the study, and for patients who permanently discontinue study drug (and are not lost to follow-up), every effort will be made to continue to collect data after discontinuation as outlined in Section 8.3.2. Where missing data exist for primary and key secondary efficacy endpoints at a minimum, imputation will occur.

Where the endpoint is a binary or categorical outcome, the imputation will occur on the binary/categorical outcome.

The following data imputation methods will be employed:

Table 13. Data Imputation Methods

Estimand	Handling Strategy: Imputation
Primary and Key Secondary Efficacy Endpoints	
Main Estimand	• Composite Strategy: Set to baseline (BOCF)

Estimand	Handling Strategy: Imputation
	• Hypothetical Strategy: Set to missing and impute with Markov Chain Monte-Carlo (MCMC) multiple imputation (MI) • Missing data not affected by ICE: MCMC MI
Second Estimand: Categorical Endpoints	• Composite Strategy: Set to non-responder (NRI) • Missing data not affected by ICE: NRI
Other Secondary and Other Efficacy Endpoints	
Estimand for Categorical Endpoints	• As per main estimand for primary and key secondary efficacy endpoints
Main Estimand for Continuous Endpoints	• As per main estimand for primary and key secondary efficacy endpoints
Second Estimand for Continuous Endpoints	• Hypothetical strategy: Set to missing and do not impute (MMRM) • Missing data not affected by ICE: do not impute (MMRM)

Abbreviations: BOCF = Baseline-Observation-Carried-Forward; ICE = Intercurrent Event; MCMC = Markov-Chain Monte-Carlo; MI = Multiple Imputation; NRI = Non-Responder Imputation; MMRM, Mixed Effect Model for Repeated Measures.

Where imputation occurs, imputation will be based on the overall population, and subsequent subgroup analyses (dupilumab naïve and previously exposed to dupilumab) will utilise these imputed data, selecting only the required patients for the analysis.

Where missing data are to be imputed for efficacy using the approaches above, a summary table by visit of the frequency and type of missing data will be presented.

The number of imputations and the seed to be used, plus any further details required, will be detailed in the SAP.

11.11 Multiplicity Strategy

No control for multiplicity between the primary and secondary variables will be taken into account. Please see Section 11.8.1.1 for the strategy of analysis for the primary and key secondary efficacy endpoints.

11.12 Interim Analysis

No interim analyses are planned.

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 computerised systems to be used to ensure the confidence in the reliability, quality, and integrity of the patient data.

Sponsors, CROs, and other authorised 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 patient by qualified and authorised 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 authorised data originators (ie, persons, systems, devices, and instruments) should be developed and maintained by PPD and made available at each clinical site

The eCRF is an auditable electronic record of information reported to the Sponsor on each trial patient, 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 recordkeeping.

The trial data sources are outlined below:

- Signed ICFs/IAFs
- Patient 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 printout, trial progress notes of the physician, reason for withdrawal, dose, contraception methods, change in child bearing potential)
- Efficacy assessments - Clinical signs: EASI, IGA, BSA; Clinical signs and Patient Reported Symptoms: SCORAD; AD Patient Reported Symptoms: Pruritus NRS, Sleep-loss scale, Skin Pain NRS, POEM; QoL and impact of disease: DLQI/CDLQI, DLQI-R, WHO-5, RECAP, and TSQM-9.
- Safety assessments – AEs, vital signs, physical examinations, clinical laboratory assessments (haematology, coagulation, serology, chemistry, urinalysis, and serum/urine pregnancy test for WOCBP).
- CCI
- Images - photographs of upper and lower body including face, hands, and limbs from a subset of patients
- Patient e-diaries
- 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 patient before the data are archived or submitted. Use of electronic signatures must comply with part 11 (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 patient's hospital chart(s), nurses' notes.

Direct Entry of Data Into the eCRF

The direct entry of data can eliminate errors by not using a paper transcription step before entry into the eCRF. For the following data elements, the eCRF is the source:

1. Inclusion and exclusion criteria confirmation
2. EASI, IGA, BSA, and SCORAD for Investigator; SCORAD, Pruritus NRS, Sleep-Loss Scale, Skin Pain NRS, POEM, DLQI/CDLQ1, WHO-5, TSQM-9 and RECAP for subjects

   Note: Central laboratory portal is the source for laboratory results and the photography vendor portal is the source for photographs.
3. Randomisation number
4. 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 the patient 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-case report form entered external data (ie, images, biomarkers, etc.) will not be loaded into the eCRF, but it will be integrated in SAS datasets and reconciled frequently with the eCRF data by PPD Data Management (DM).

The source data verification will be performed by PPD CRA (monitor) according to the requirements specified in the Monitoring Plan.

At the trial end, PPD will generate 1 certified "true copy" of the completed case report form at the site and will send to the Investigator(s) that copy certification together with the completed eCRFs (in portable document format [PDF]) from all patients enrolled at his or her location.

12.1.3 Patient 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 patients at

the Screening visit and as many times as deemed necessary. Patients will also receive written instructions on the Study App use and reminders, including but not limited 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 patient.

When an instrument is used by a patient or Investigator to transmit patient data elements directly to the eCRF, the patient or Investigator is the data originator and the eCRF is the source of data. If a process is used by which the patient 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 patients completing the PRO questionnaires and a diary. The patients will be asked to have the Study App on their own mobile phone. There will also be the possibility to provide patients with a mobile phone, if necessary.

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

- SCORAD (only those questions addressed to patients)
- Pruritus NRS
- Sleep-loss
- Skin pain NRS
- DLQI or CDLQI
- WHO-5
- RECAP
- TSQM-9
- POEM

Patients will also record use of TCS and study drug intakes in the Patient Diary as applicable.

The Study App recording will be transferred to the database.

The Study App will work across all smartphones.

At the study end the Investigator will receive a CD/DVD/USB drive with the mobile application data (in PDF format) from the patients enrolled at his/her location. The Investigator will keep this CD 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 authorise representatives of appropriate Competent Authorities.

12.2 Data Management and Quality Control

DM of the trial will be performed by the PPD DM department and supervised by the Sponsor's DM department, according to the Sponsor and PPD SOPs.

To facilitate the collection of accurate and complete data, PPD 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 PPD 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 PPD 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 (including rescue medications) will be coded; the Medical Dictionary for Regulatory Activities and WHO-DRUG Enhanced 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 Patient Diary data from the patients 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 PPD 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, case report forms, 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 PPD and/or vendors (eg, eCRF, laboratories), to train PPD staff on trial procedures.

An Investigators' meeting will be performed, including training on GCP procedures, trial protocol, efficacy 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 PPD to assess whether 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 PPD according to the details specified in the Monitoring Plan.

The trial CRA(s) 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 case report forms, 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/IAF signed by the patient (or parents/caregivers, if applicable) and maintain source documents for each patient in the trial, case and visit notes medical records, all information on case report forms must be traceable to these source documents in the patient´s file.

A close out visit to solve pending issues and to agree on the shipment of remaining trial materials to the Sponsor (eCRF/case report forms and other data source, medication) will be performed by the trial CRA once all patients 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/IAF 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 human patients 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 patient to protocol procedures concerning their duties in the trial.

The Investigator, PPD /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, PPD and the Sponsor will work according to the ICH guidelines, the 21 CFR of the European Directive 2001/20/EC.

The Investigator shall administer the trial medication to patients 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 patient's compliance throughout the trial.

At the completion of treatment (or premature discontinuation) patients 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 patient's family practitioner or specialist that usually treats his/her condition

14.2 Patient Information and ICF/IAF

Patients 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 patients 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 patient is otherwise entitled. Administration of the drug may be interrupted, and a patient withdrawn from the trial at the discretion of the Investigator. The Investigator should justify his decision in the patient's eCRF.

Any patient 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 ICF/IAF in writing before starting any trial procedure by signing the ICF/IAF, which must be dated by the patient and the Investigator. At such time the patient must be given adequate time to understand the information provided and ask questions, if required. A copy of the signed ICF/IAF will be given to the patient. The original shall be kept on file by the Investigator. Any new relevant information that becomes available during the trial will be provided to the patient.

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 authorised by Almirall, S.A. and approved by the relevant IEC before use.

After the completion of the trial, lay summaries summarising main results from the trial will be make available for patients.

14.3 Independent Ethics Committee or Institutional Review Board Review

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

The Sponsor or PPD must promptly report to the IEC all changes in research (protocol amendments) and will not make such changes without IEC approval except where necessary to eliminate apparent immediate hazards to the trial patients or administrative changes.

SAEs reasonably related to the study drug will be communicated by the Investigator,PPD to the IEC.

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

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

14.4 Patient Data Protection

The trial patients 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 patient diary), patients will be identified only by the assigned patient identification number and year of birth.

A signed written ICF/IAF signifies the explicit acceptance by the individual that data from the trial will be available to the Investigator and his/her staff, the authorised representatives of the Sponsor and, if required, by the IEC and Competent Authorities. However, all data contained in the patient'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.

15 Financing and Insurance

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

All patients 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 patients 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 recognised public databases, such as clinicaltrials.gov in the US and EudraCT in the European Union.

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, the members of the staff and the patients 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/or US Food and Drug Administration regulatory compliance obligations, and only after mutual agreement between the Investigator and the Sponsor.

17 Other Practical Considerations

17.1 Investigator's Brochure

The IB contains a summary of the preclinical and clinical. The same confidentiality procedures apply as for the IB and protocol.

The IB will be included in the Investigator's file. The Investigator will sign a receipt form.

17.2 Final Clinical Trial Report

The CSR will be written by PPD 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 PPD and/or the Sponsor before issuing the final version.

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 Amendments

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. 2 types of amendment maybe produced:

- Substantial Amendments (related to the safety or physical or mental integrity of the patients, 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 and/or Competent Authorities and approved by them before implementation.
- Nonsubstantial 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.

17.5 COVID-19

Given the current COVID-19 pandemic, per regulatory guidance, a listing of patients either experiencing COVID-19 or at least possibly affected by COVID-19–related measures will be produced where applicable. In addition, a COVID-19 Visit Impact CRF has been included. Further details relating to additional populations and subgroup analyses, handling of protocol deviations, handling of missing data (including use of virtual assessments and/or switches from local to centralised labs), and any other considerations related to COVID-19 and related measures will be detailed further in the SAP, to be finalised before unmasking.

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Appendix 1. Hanifin/Rajka Diagnostic Criteria for Atopic Dermatitis

Appendix 2. Provisions for Changes in Study Conduct During Exceptional Circumstances

Appendix 1. Hanifin/Rajka Diagnostic Criteria for Atopic Dermatitis

To establish a diagnosis of atopic dermatitis, the patient requires the presence of at least 3 "basic features" and 3 or more minor features listed below.

Basic Features

Must have 3 or more basic features:

- Pruritus
- Typical morphology and distribution
- Flexural lichenification or linearity in adults
- Chronic of chronically-relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Features

Plus, 3 or more minor features:

- Xerosis
- Ichthyosis, palmar hyperlinearity, or keratosis pilaris
- Immediate (type 1) skin-test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency toward cutaneous infections (especially Staph. Aureus and Herpes simplex)/impaired cell-mediated immunity
- Tendency toward non-specific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental or emotional factors
- White dermographism/delayed blanch

Appendix 2. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the Sponsor in partnership with the Investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the Investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the Sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards (ERBs), regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

If the Sponsor grants written approval for changes in study conduct, the Sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

Additional consent/assent from the participant will be obtained, as applicable, and/or as required by ERB's and local regulations. Assent will also be obtained to the same parameters, with consent for participants reaching the legal age for consent during the trial for continued participation, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- a change in the method of study drug administration,
- dispensation of additional study drug during an extended treatment period,
- alternate delivery of study drug and ancillary supplies, and

- provision of their personal or medical information required before implementation of these activities.

Changes in Study Conduct During Exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

1. Remote visits

The study site should capture specific explanation for any missing data and other protocol deviations in source documents. While protocol deviations may be unavoidable in an exceptional circumstance, documentation of protocol deviations and missing data will be important for data analysis.

The following visits cannot be conducted remotely because efficacy or safety assessments must be performed in person at these visits:

- Screening
- Baseline (Day 1), and
- Week 16.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to:

- AE and SAE reports
- concomitant medications
- Dermatology Life Quality Index/Children's Dermatology Life Quality Index (DLQI/CDLQI)
- compliance with the participant eDiary, and
- self-administration of study drug, if needed, and recording the self-administration details in the Study Drug Administration Log. Before administering study drug at home, participants and/or parents or caregivers will be adequately trained on at home study drug administration; see also the section "Study drug and ancillary supplies (including participant diaries)" below.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site, when participants cannot travel to the site because of an exceptional circumstance, if written approval is provided by the Sponsor. Procedures performed at such visits include, but are not limited to:

- taking blood samples

- collecting urine samples for pregnancy testing
- assessing the amount of the topical corticosteroid (TCS) use
- conducting physical assessments
- administering patient-reported outcomes
- administering study drug, and
- collecting health information.

2. Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for the following samples:

- Pharmacokinetic
- Immunogenicity
- Testosterone
- Oestradiol

The local laboratory must be qualified in accordance with applicable local regulations. Clinically significant laboratory findings will be reported as an AE in the AE electronic case report form (eCRF).

3. Study drug and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the Sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff
- without completion of a full study visit,
- asking the participant's parent/caretaker or designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies, and
- working with the Sponsor to determine how study drug that is typically administered on site will be administered to the participant; for example, self-administered or administered during a mobile healthcare visit.
- returning the TCS tubes to the study staff

These requirements must be met before action is taken:

- Participants or their parents/caregivers are appropriately trained on at home administration of the study drug (unless they have already received that training); the mobile healthcare provider will observe the participant or caregiver administer the study drug for the first time.
    - If the study drug is administered at home, participants or their parents/caregivers will need to record the details about the injections in the patient diary (regardless of whether the at home study drug administration is done by the participant him-/herself, caregiver, or mobile healthcare provider). For the at home administration information under exceptional circumstances, the Study Drug Administration Log will be used.

- Alternate delivery of study drug should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (eg, participant's home), the Investigator, Sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant and the participant's parent/caregiver or designee on the final disposition of any unused or completed study supplies.

Unless the study drug is self-administered by the trained participants or their parents/caregivers, only authorised study personnel may supply, prepare, or administer study drug during a mobile healthcare visit.

4. Screening Period guidance

If the study Screening window exceeds 4 weeks because of the exceptional circumstances, the participant would be considered a screen failure and documented as such in the eCRF. The participant may be rescreened once. If rescreening is required more than once, it must first be approved by the Sponsor.

The Screening procedures per the Schedule of Visits and Procedures in the protocol should be followed to ensure participant eligibility for the study. Before rescreening, the participant must sign a new ICF/IAF and receive a new identification number.

5. Adjustments to visit windows

Whenever possible and safe to do so, as determined by the Investigator's discretion, participants should complete the usual Schedule of Visits and Procedures. To maximise the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the Sponsor. This minimises missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows. Subsequent dosing should be a minimum of 7 days apart if the visit window is expanded because of exceptional circumstances.

Visit	**Tolerance**
Weeks 2 through 14	±7 days
Week 16	-7/+14 days
Week 68 (18-week SFU)	-7/+14 days

For participants whose visits have extended windows, additional study drug may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study drug and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the Investigator's source documentation and should be transferred to the site in a secure and timely manner.

M-17923-30 Protocol_Global Amendment 2_clean 22Aug2022

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	PPD	30-Aug-2022 09:51 GMT+0
PPD	PPD	30-Aug-2022 09:53 GMT+0
PPD	PPD	31-Aug-2022 12:47 GMT+0

eDMS R&D Object_ID: CCI