Statistical Analysis Plan for Interventional Studies

Text only

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Sponsor Name: Almirall, S.A.

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Authors: PPD
PPD

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Revision History

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1.0	21-Dec-2022	PPD PPD	Initial Release Version
2.0	22-Mar-2023	Version revised by Almirall (PPD)	SAP Amendment #1. SAP has been amended according to Local protocol amendment 4 for Germany. Sections that have been changed are: 2.2 Timings of Analyses, 3. Study Objectives and Endpoints, 4.1.4. Extension Period for Germany according to Protocol amendment 4, 4.1.5. Safety Follow-up Visit, 4.6. Study Procedures and Flowchart, 9.6. Maintenance Period (and Extension period for patients from Germany) Analyses, 10. Safety. Also, in section 8.7. Extent of Exposure - the exposure for patients in Placebo who complete the Maintenance Period has been corrected. In section 8.8 Treatment Compliance – the formula for treatment compliance calculation has been added for clarity. It has been specified that the analyses of the endpoint 4point NRS pruritus improvement will be based on those patients within FAS who had a baseline NRS pruritus score more or equal than 4, that the analyses of the endpoint 4point NRS Skin pain improvement will be based on those patients within FAS who had a baseline NRS skin pain score more or equal than 4 and that the analyses of the endpoint 4point DLQI improvement will be based on those patients within FAS who had a baseline DLQI score more or equal than 4, It has been added a footnote to the Table in section 9.6 Maintenance Period (and Extension period for patients from Germany) Analyses. Finally in section 10.1, the wording of TEAE definition has been modified by deleting "increased in frequency" since frequency is not needed to take into account for the TEAE derivation.

I confirm that I have reviewed this document and agree with the content.

Approvals

PPD Health Approval

PPD	PPD	Mar 23, 2023
Name, Title PPD	Signature Electronically signed by: PPD Reason: I am the author Date: Mar 23, 2023 07:3[illegible] GMT+9	Date (DD-Mmm-YYYY)
PPD	PPD	Mar 23, 2023
Name, Title PPD	Signature Electronically signed by: PPD Reason: I am the reviewer Date: Mar 23, 2023 09:2[illegible] GMT+1	Date (DD-Mmm-YYYY)
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Name, Title PPD	Signature Electronically signed by: PPD Reason: I am the reviewer Date: Mar 23, 2023 09:23 GMT	Date (DD-Mmm-YYYY)

Almirall Approval

PPD	PPD	Mar 23, 2023
Name, Title PPD	Signature Electronically signed by: PPD Reason: I am the approver Date: Mar 23, 2023 16:51 GMT+1	Date (DD-Mmm-YYYY)

Table of Contents

Revision History 2
Approvals 3
1. Glossary of Abbreviations 8
2. Purpose 11
2.1. Responsibilities 11
2.2. Timings of Analyses 11
3. Study Objectives and Endpoints 12
4. Study Design 16
4.1. Brief Description 16
4.1.1. Screening period 16
4.1.2. Baseline and Double-Blinded Induction Period (week 0 to week 16) 16
4.1.3. Maintenance Period (week 16 to week 52) 16
4.1.4. Extension Period for Germany according to Protocol Amendment 4 16
4.1.5. Safety Follow-up Visit 16
4.2. Patient Selection 17
4.2.1. Inclusion Criteria 17
4.2.2. Exclusion Criteria 17
4.3. Determination of Sample Size 17
4.4. Treatment Assignment and Blinding 17
4.5. Administration of Study Medication 18
4.6. Study Procedures and Flowchart 19
5. Analysis Sets 22
5.1. Full Analysis Set 22
5.2. Safety Analysis Set 22
5.3. Per Protocol Set 22
5.4. Protocol Deviations 22
6. Estimands and Data Handling for Efficacy Analyses 23
6.1. Primary Efficacy Analysis (Overall Population) 23
6.1.1. Primary and Key Secondary Efficacy Endpoints 23
6.1.2. All Other Secondary and Other Efficacy Endpoints 24

6.2. Subgroup Efficacy Analyses (Dupilumab Naïve and Patients Previously Exposed to Dupilumab) 25
6.3. Imputation Process for Estimand Handling and Missing Data 25
6.3.1. General Multiple Imputation Approach 26
6.3.2. Nonresponder Imputation 27
6.3.3. Mixed-effects Model for Repeated Measures 27
7. General Aspects for Statistical Analysis 28
7.1. General Methods 28
7.2. Key Definitions 28
7.2.1. First Dose Date 28
7.2.2. Last Dose Date 28
7.2.3. Study Day 28
7.2.4. Baseline and Change from Baseline 28
7.3. Missing Data 29
7.3.1. Partial or Missing Event Dates 29
7.3.2. Adverse Events 29
7.3.3. Prior/Concomitant Medications 30
7.4. Visit Windows 30
7.5. Adjustments for Covariates 31
7.6. Subgroups 31
7.7. General Considerations for Efficacy during Induction Period 31
7.8. General Considerations for Efficacy during Maintenance Period 31
7.9. Control for multiplicity 32
8. Demographic, Other Baseline Characteristics and Medication 33
8.1. Patient Disposition and Withdrawals 33
8.2. Protocol Deviations 33
8.3. Demographic and Baseline Characteristics 33
8.4. Medical History and Concomitant Diseases 34
8.5. Other Baseline Characteristics 34
8.6. Medication 34
8.6.1. Prior Medication 34
8.6.2. Concomitant Medication 34

8.6.3. Post Medication 34
8.6.4. Rescue Medication 35
8.7. Extent of Exposure 35
8.8. Treatment Compliance 36
9. Efficacy 37
9.1. Statistical Hypotheses 37
9.2. Definitions for Efficacy Endpoints 37
9.3. Analysis of the Primary and Key Secondary Efficacy Endpoints 47
9.4. Analysis of all Other Secondary and Other Efficacy Endpoint 48
9.5. Subgroup Efficacy Analyses (Dupilumab Naïve and Patients Previously Exposed to Dupilumab) 49
9.6. Summary of the Statistical Efficacy Analysis to be performed with Induction period data 49
9.7. Maintenance Period (and Extension Period for Patients from Germany) Analyses 54
10. Safety 55
10.1. Adverse Events 55
10.2. Laboratory Evaluations 56
10.3. Vital Signs 56
10.4. Physical Examination 57
10.5. Special Safety Topics including Adverse Events of Special Interest 57
10.5.1. Eosinophilia and Eosinophil-Related Disorders 57
10.5.2. Infections, Including Herpes Infections and Relevant Parasitic Infections 57
10.5.3. Conjunctivitis 58
10.5.4. Hypersensitivity 58
10.5.5. Injection Site Reactions (ISR) 58
10.5.6. Malignancies 59
10.5.7. Atopic Dermatitis Exacerbation 59
11. Changes from Analysis Planned in Protocol 60
12. Reference List 61
13. Programming Considerations 62
13.1. General Considerations 62
13.2. Table, Figure, and Listing Format 62

13.2.1. General 62
13.2.2. Headers 62
13.2.3. Display Titles 63
13.2.4. Column Headers 63
13.2.5. Body of the Data Display 63
13.2.6. Footnotes 65
14. Quality Control 67
15. Appendices 68

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AD	Atopic dermatitis
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
BOCF	Baseline-Observation-Carried-Forward
BSA	Body Surface Area
CI	Confidence Interval
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CsA	Cyclosporine A
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
DLQI-R	DLQI-Relevant
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICE	Intercurrent Event
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
ISR	Injection site reaction
Max	Maximum
MCMC MI	Markov Chain Monte-Carlo Multiple Imputation
MMRM	Mixed Effect Model for Repeated Measures

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
NA	Not Applicable
NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
OI	Opportunistic infection
OR	Odds Ratio
POEM	Patient-Oriented Eczema Measure
PPS	Per Protocol Set
PRO	Patient-Reported Outcome
PT	Preferred Term
QC	Quality Control
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QoL	Quality of life
RECAP	Recap of atopic eczema
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
WHO-5	World Health Organization – Five Well-Being Index

Abbreviation	Description
WOCBP	Women of childbearing potential

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

PPD will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

Study results will be delivered in 4 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,

The second results delivery will be provided after second database lock, once all patients have completed week 52, or discontinued before this point, and

The third results delivery will be provided after the third database lock, at the end of the study, once all patients (excluding those patients who joined the German extension) have completed the study including follow-up (week 68) or discontinued before this point.

Finally, the fourth delivery will be provided after the German extension completion (according to Local Protocol Amendment number 4 for Germany (dated 2-Feb-2023)).

Accordingly, 4 different database locks will be performed. A full CSR including Induction Period and Maintenance Period, and an addendum which will also cover the follow-up starting after week 52 until week 68 plus the German extension period.

3. Study Objectives and Endpoints

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

	CCI [redacted]

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 IGA 0/1 and 2-point improvement (by week, between Week 16 and Week 52). - Percentage of patients achieving a 4-point improvement Pruritus NRS (by week, between Week 16 and Week 52). - Percentage of patients achieving EASI 75, EASI 90, EASI 50 (by week, between Week 16 and Week 52) - Percentage of patients achieving a 4-point improvement in DLQI/CDLQI (by week, between Week 16 and Week 52). - Percentage of patients achieving a 4-point improvement Skin Pain NRS (by week, between Week 16 and Week 52). - Change from Baseline BSA (by week, between Week 16 and Week 52). - Change from Baseline SCORAD (by week, between Week 16 and Week 52). - Change from Baseline Pruritus NRS (by week, between Week 16 and Week 52). - Change from Baseline sleep loss (by week, between Week 16 and Week 52). - Change from Baseline POEM (by week, between Week 16 and Week 52). - Change from Baseline DLQI/CDLQI (by week, between Week 16 and Week 52). - Change from Baseline Skin Pain NRS (by week, between Week 16 and Week 52) - Proportion of TCS-free days from Baseline (by week, between Week 16 and Week 52) - Time to TCS-free use (days) -
	Exploratory Endpoints: CCI [redacted]
	Safety and Tolerability Endpoints
To evaluate the safety and tolerability of lebrikizumab in patients not adequately	- Incidence of AEs up to and including Week 16. AEs includes TEAEs, SAEs, Related

controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 16	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 52/68	- Incidence of AEs up to and including Week 52/68. 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.
For patients entering the Extension Period, to evaluate the long-term efficacy, safety, and tolerability of lebrikizumab in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to end of trial in Germany (according to local protocol amendment 4 for Germany)	- Percentage of patients achieving EASI 75, EASI 90, EASI 50; IGA 0/1 and 2-point - Improvement, and 4-point improvement Pruritus NRS by visit. - Change from Baseline in BSA, SCORAD, Pruritus NRS, sleep loss, DLQI/CDLQI, and Skin Pain NRS by visit. - Percentage of patients achieving a 4-point improvement in DLQI/CDLQI by visit. Incidence of AEs by visit. 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) by visit. - Observed results and changes from Baseline in Vital Signs Results by visit. - Percentage of patients with abnormalities in physical examination by visit.
Exploratory Objectives	**Other Endpoints**
CCI [redacted]	

CCI [redacted]	

[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.

4. Study Design

4.1. Brief Description

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.

4.1.1. Screening period

The Screening Period will start with the Screening visit and continue until randomisation. Electronic diary collection will begin at screening.

4.1.2. Baseline and Double-Blinded Induction Period (week 0 to week 16)

At baseline visit (Day 1), patients who meet the study eligibility criteria will be 2:1 randomly assigned to their induction treatments with stratification based on previous use of dupilumab (Yes / No), age (adolescent patients ≤12 to <18 versus adults ≥18 years) and baseline disease severity (IGA 3/ IGA 4).

The treatment groups in the Blinded Induction Period are:

- Lebrikizumab 250 mg every 2 weeks (Q2W): 500 mg lebrikizumab administered at Baseline and Week 2 (loading dose)
- Placebo by Subcutaneous (SC) injection Q2W

4.1.3. Maintenance Period (week 16 to week 52)

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 open label 1 injection of lebrikizumab 250 mg every 2 weeks (Q2W).

4.1.4. Extension Period for Germany according to Protocol Amendment 4

According to Local protocol amendment 4 for Germany (dated 2-Feb-2023), Extension Period treatment duration is a minimum of 6 months (24 weeks) following Week 52 and until lebrikizumab is commercially available in Germany. Maintenance dose changed to once every 4 weeks (Q4W) during the Extension Period, with return to once every 2 weeks (Q2W) allowed at the Investigator's discretion.

4.1.5. Safety Follow-up Visit

Patients who terminate early from the study or do not enroll in the long-term extension study, will undergo a follow-up visit approximately 18 weeks (4 weeks for patients in Germany who joined Extension period) after the last study drug injection.

4.2. Patient Selection

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

Adolescent patients (aged ≥12 to <18 years weighing ≥40 kg) will be included and will receive the same doses of lebrikizumab as for adults (adolescent patients aged ≥12 to <18 years will make up 12.5% of the overall population compared to adults aged ≥18 years).

4.2.1. Inclusion Criteria

Patients eligible for inclusion in this trial must fulfil all criteria described in section 8.2 of protocol.

4.2.2. Exclusion Criteria

Patients fulfilling any of the criteria described in section 8.3 of protocol are not eligible for inclusion in this trial.

4.3. Determination of Sample Size

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.

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 also 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. A two-sided type one error of 5% has been assumed.

4.4. Treatment Assignment and 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. 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.

4.5. Administration of Study Medication

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. 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 doubleblind, 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.

4.6. Study Procedures and Flowchart

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[j]		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[j,k], Sleep-loss scale[j,k], Skin Pain NRS[j,k]	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
POEM, RECAP[k]		X		X		X		X		X
DLQI or CDLQI, DLQI-R[k]		X	X	X		X		X		X
WHO-5[k]		X								X
TSQM-9[k]		X								X
Photography[k]		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[a]

Study Procedures	Maintenance Period																		Safety Follow-up Visit[a,n]
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[b]
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[k]								X										X	
DLQI or CDLQI, DLQI-R[l]				X				X										X	
WHO-5[l]								X										X	

Study Procedures	Maintenance Period																		Safety Follow-up Visit[a,n]
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[b]
Visit window[d]	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d	±5d
TSQM-9[k]								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		
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), except for patients who continue treatment in the Extension Period.
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.
n. Only applicable to patients who do not enter the Extension Period.

Only for German Extension according to Local Protocol Amendment 4 for Germany

Extension Period and Safety Follow-up Visit for Patients who Enter the Extension Period

Study Procedures	Extension Period							Safety Follow-up Visit[a]
Study Visit	EXT 1[c]		EXT 2	EXT 3	EXT 4[p]	EXT 5[p]	EXT 6[p,q]	EXT SFU (4 weeks after last lebrikizumab dose)
Timing (weeks) relative to Week 52 (Visit 28)	0 to ≤4	>4 to 6						
Timing (weeks) relative to EXT 1 visit	-	-	+12	+24	+36	+48	+60	
Visit window[d]	NA	NA	±10d	±10d	±10d	±10d	±10d	+10d
Vital signs		X	X	X	X	X	X	X
Physical examination, height, weight, BMI[e]		X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X
Haematology, chemistry[f]		X		X		X		X
Urinalysis		X		X		X		X
Pregnancy test, contraception check[g,h]	X[o]	X	X	X	X	X	X	X
IGA, EASI, BSA		X	X	X	X	X	X	X
SCORAD		X		X		X		X
Pruritus NRS[i,j]		X	X	X	X	X	X	X
Skin Pain NRS[i,k], Sleep-loss scale[i,k]		X	X	X	X	X	X	X
E-Diary: POEM, RECAP[i]		X		X	X	X	X	X
DLQI or CDLQI, DLQI-R[i]		X		X	X	X	X	X
WHO-5[i]		X		X	X	X	X	X
TSQM-9[i]		X		X	X	X	X	X
Photography[q]				X		X		X
Administer/Dispense study drug and Product Complaint reporting[c,l]	X	X	X	X	X	X	X	
Assess treatment compliance[m]			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; 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 and final assessment visit will occur 4 weeks after the last dose of study medication in patients who enter the Extension Period.
b. After the EXT 6 visit, any subsequent visit(s) will be conducted every 12 weeks until lebrikizumab is commercially available in Germany and EXT 3 visit assessments will be performed at any of those subsequent visit(s), except haematology, chemistry, and urinalysis and photography which will be performed every 24 weeks.
c. Beginning at Week 52 (or within 8 weeks of the last dose of lebrikizumab in the Maintenance Period [Week 50]), patients entering the Extension Period will be treated with lebrikizumab 250 mg every 4 weeks (Q4W), for at least 6 months (24 weeks). According to the Investigator's judgement, the lebrikizumab dosing frequency during the Extension Period may be increased to Q2W at any time in patients not maintaining clinical benefit but may not thereafter be decreased again to Q4W.
d. Visit window for patient-reported outcomes is -10 days during Extension Period.
e. For adults, height is only captured at screening.
f. 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. Urine pregnancy test for WOCBP during the Extension Period. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period. Male subjects engaged in a relationship with a WOCBP must be contacted 4 weeks after last dose of study medication in the Extension Period 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.
j. To be performed every 2 weeks during the Extension Period.
k. To be performed every 4 weeks during the Extension Period.
l. Sufficient drug is dispensed to cover injections through next visit.
m. Compliance assessment for study drug as well as accountability.
n. The study will conclude when all patients entering the Extension Period have been treated for at least 6 months (24 weeks), or discontinued prior to this point, and lebrikizumab is commercially available in Germany. Therefore, a given patient may have more than 3 site visits during the Extension Period.
o. Patients who complete Week 52 of the Maintenance Period will be given the opportunity to continue lebrikizumab treatment in the Extension Period. The first visit in the Extension Period (EXT 1, ie start of treatment in the Extension Period) may coincide with the Week 52 visit of the Maintenance Period or the first Extension Period visit may occur up to 8 weeks from the last dose administration in the Maintenance Period (Week 50). If the gap between the Week 52 visit and the first Extension Period visit (EXT 1) is 0 to ≤2 weeks (ie, up to 4 weeks after the Week 50 lebrikizumab dose), then efficacy and safety assessments (except pregnancy testing) do not need to be repeated and these assessments will be taken from the Week 52 visit. Pregnancy testing must be repeated in women of childbearing potential (WOCBP), unless the Week 52 visit coincides with the first Extension Period visit. If the gap between the Week 52 visit and the EXT 1 visit is >2 to ≤6 weeks (EXT 1 yellow shaded area, ie, >4 to ≤8 weeks after the Week 50 lebrikizumab dose), then efficacy and safety assessments must be repeated at the EXT 1 visit.
p. Green shaded EXT 4, EXT 5, and EXT 6 visits are applicable only to patients who continue treatment beyond EXT 3 either because not all patients entering the Extension Period have had at least 6 months (24 weeks) of treatment or lebrizumab is not yet commercially available in Germany and, therefore, the Extension Period has not yet ended.
q. For patients who consent at selected sites.

5. Analysis Sets

Three different statistical analysis sets have been defined in this study:

5.1. Full Analysis Set

The Full Analysis Set (FAS) will include all randomised patients. Patients will be analysed under the treatment group as randomised. The FAS will be used for all analyses of efficacy endpoints as well as for demographics and baseline characteristics.

5.2. Safety Analysis Set

The Safety Analysis Set (SAF) will include all randomised patients who receive at least 1 dose of the study drug. Patients will be analysed under the treatment group actually received. The SAF will be used for all analyses of safety endpoints.

5.3. Per Protocol Set

The Per Protocol Set (PPS) will include 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 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.

5.4. 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. Protocol deviations are categorized as non-important or important and finalized during BDRM before database lock.

Protocol deviations affecting primary efficacy will be defined and reviewed before the BDRM and closed during the BDRM, to be held (with report finalized) before database lock.

All patients enrolled (those who signed the inform consent) will be described in the summaries of patient disposition, and will be used will be used for some patient listings.

6. Estimands and Data Handling for Efficacy Analyses

As discussed in Protocol Section 11.8.1, 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. As CCI , all efficacy endpoints will be analysed as well by previous exposure to dupilumab (Yes/No).

6.1. Primary Efficacy Analysis (Overall Population)

6.1.1. 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 below:

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 patients achieving EASI 75, IGA criteria, pruritus NRS criteria at Week 16

Abbreviations: AD = atopic dermatitis; EASI = Eczema Area and Severity Index (score); IGA = Investigator Global Assessment; NRS = Numerical Rating Scale.

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

Treatment discontinuation due to pandemic will be treated under the same intercurrent event as treatment discontinuation due to reasons other than lack of efficacy. Intermittent missing assessment due to pandemic and/or related restrictions will be treated the same as any other intermittent missing values. Details of how missing data will be handled for efficacy are described in Section 6.3.

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.

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
Second Estimand: Categorical Endpoints (Composite)	Composite Strategy: Set to non-responder	Composite Strategy: Set to non-responder	Composite Strategy: Set to non-responder

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

Details on missing data imputation are described in Section エラー! 参照元が見つかりません。.

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.

6.1.2. All Other Secondary and Other Efficacy Endpoints

All binary other secondary and other efficacy endpoints will be analysed using the same methodology as described in Section 6.1.1 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:

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
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.

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

The same estimands as per Section 6.1 will also be conducted for the subgroup analyses, for CCI purposes.

6.3. Imputation Process for Estimand Handling and Missing Data

Imputation for missing data will occur for primary and key secondary efficacy endpoints.

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:

Estimand	Handling Strategy: Imputation
Primary and Key Secondary Efficacy Endpoints	
Main Estimand	• Composite Strategy: Set to baseline (BOCF) • 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: ICE = Intercurrent Event; MCMC = Markov-Chain Monte-Carlo; MI = Multiple Imputation; BOCF, Baseline-Observation-Carried-Forward; 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 week of the frequency and type of missing data will be presented.

General MI Approach (Section 6.3.1) will be used for

- Main estimand of the primary and key secondary efficacy endpoints
- Main estimand for categorical other secondary efficacy endpoints
- Continuous Other Secondary Efficacy Endpoints

Non-Responder Imputation Approach (Section 6.3.2) will be used for the Second estimand of the primary and key secondary efficacy endpoints.

Mixed Model for Repeated Measures analyses (Section 6.3.3) will be performed on second estimand for continuous other secondary efficacy endpoints.

6.3.1. General Multiple Imputation Approach

The primary method of imputation for missing data will be MI (Multiple Imputation); the MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. Total EASI score will be imputed in this manner.

For the imputation of the primary endpoint, where a MI approach is described, the continuous EASI score between 0 and 72 will be multiple imputed, and subsequently the (percentage) change from baseline will be calculated for each imputation in order to derive the categorical outcome of EASI 75. The number of imputations will be 100 for the MI step, representing the set of 100 plausible values obtained from a prediction model based primarily on observed data. The number of imputations and/or burn-in iterations may be increased if there are convergence issues.

Note that all patients in the FAS will be included in the imputation steps below. As previous dupilumab exposure is one of the stratification factors to be included in the MI models, imputation will be in part based on this factor. For analysis, the specific population will then be selected from this total pool of FAS patients with complete data.

The full MI approach will comprise steps as follows:

- Composite Variable Strategy Step (1 imputation): Any missing data to be handled using a composite variable strategy will be imputed using a BOCF approach.
- Multiple imputation Step (100 imputations): After setting to missing any data to be handled using a hypothetical strategy, impute any missing data with a Markov Chain Monte-Carlo (MCMC) multiple imputation approach.
- Combining Step: Rubin's rule (SAS PROC MIANALYZE) is used to combine the 100 point estimates and standard errors, in order to provide a single point estimate, confidence interval and p-value that can be compared to the respective null hypotheses to provide rejection or acceptance.

6.3.1.1. BOCF Approach for Composite Variable Handling Strategy

Monotone missing data implementing the composite variable strategy will be imputed using a BOCF approach, whereby any missing data occurring on or after ICE of death will be singularly imputed using the available baseline result for the patient. If no observed baseline result is immediately available, then the imputed value from Step 1 will be used and carried forward.

6.3.1.2. Markov Chain Monte-Carlo (MCMC)

Any patient with missing data for EASI score will be multiple imputed using a MCMC approach, with multiple chains, including factors for study treatment, stratification factors, baseline EASI score, and binary variables for ICE occurrence at the visit. At this point, 100 imputations will be available for the primary estimand.

Example SAS syntax is as follows:

CCI

6.3.1.3. Combining Step (Rubin's Rule)

SAS Proc MIANALYZE will be used to combine the 100 point estimates (per estimand) for the difference in percentage of patients achieving EASI 75 response at Week 16 between treatments and standard errors, allowing appropriate statistical inference as described below:

CCI

[redacted]

6.3.2. Nonresponder Imputation

The nonresponder imputation (NRI) method will be used to handle missing data relative to the supportive estimand for binary/categorical endpoints (composite). Patients who receive rescue medication or discontinue treatment, will be set to non-response subsequent to this time through Week 16. Intermittent missing values will also be set to non-response.

The nonresponder imputation (NRI) method imputes missing values as non-responders and can be justified based on the composite strategy (ICH E9R1) for handling intercurrent events. In this strategy patients are defined as responders only if they meet the clinical requirements for response at the predefined time AND they remain on the assigned study treatment (ie not using rescue medications and not having missing values due to other reasons). Failing either criteria by definition makes them nonresponders.

Randomized patients without at least 1 post-baseline observation will also be defined as nonresponders for all visits for the NRI analysis.

6.3.3. Mixed-effects Model for Repeated Measures

Mixed Model for Repeated Measures analyses will be performed on continuous endpoints to mitigate the impact of missing data. This approach assumes missing observations are missing-at-random (missingness is related to observed data) and borrows information from patients in the same treatment arm taking into account both the missingness of data through the correlation of the repeated measurements.

When MMRM is used, the model includes treatment, baseline value, visit, the interaction of the baseline value-by-week, the interaction of treatment-by-week, and the stratification factors mentioned in Section 7.5 as fixed factors.

Example SAS syntax is as follows:

CCI

[redacted]

7. General Aspects for Statistical Analysis

7.1. General Methods

- Unless otherwise specified, summaries will be presented by study period, by treatment group and overall.
- Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), standard error of mean, median, first and third quartiles, minimum and maximum. Categorical variables will be summarized using number of observations (n) and percentages (%) of patients. The 95% CI around the mean may also be presented in descriptive statistics as appropriate for specific endpoints of interest.
- All relevant patient data will be included in listings. All patients entered into the database will be included in patient data listings

7.2. Key Definitions

7.2.1. First Dose Date

First dose date is defined as the day of first dose of study treatment received after randomization.

7.2.2. Last Dose Date

Last dose date is defined as day of the last dose of study treatment.

For patients ongoing for the treatment period at time of analysis prior to database lock, the last dose date is the date of the most recent study visit where study drug was administered in the database for the patient.

7.2.3. Study Day

The study day is determined relative to the date of first dose of study treatment, unless otherwise specified. The day of the first dose of study treatment is defined as study day 1. The day prior to the first dose of study treatment is study day -1. There is no study day 0.

For events that occur before the first dose of study treatment,

study day = date of the event – first dose date;

for events that occur on or after the first dose of study treatment,

study day = date of the event – first dose date + 1.

7.2.4. Baseline and Change from Baseline

For all change from baseline variables, the baseline is defined as the last non-missing assessment prior to or on the day of randomization, and must be prior to the first administration of study treatment, including scheduled and unscheduled visits, unless otherwise specified. Hence, change from baseline = post-baseline value – baseline value.

The baseline value for analyses of qualitative parameters (e.g., normal/abnormal) is defined as the last evaluation prior to or on the day of randomization, and must be prior to the first administration of study treatment.

The baseline value for the PRO questionnaires and diary will be the average of the 7 days before starting study treatment.

7.3. Missing Data

Missing data imputation rules for efficacy data are specified in Section エラー! 参照元が見つかりません。. All other missing data not covered here will not be imputed. Analyses will be performed considering all data observed for the respective analysis sets.

7.3.1. Partial or Missing Event Dates

All partial or missing dates will be presented in the data listings as they are recorded on the electronic Case Report Form (eCRF). The analysis dataset will flag where day, month or year has been imputed for analysis start or stop date.

7.3.2. Adverse Events

For the purpose of assessing whether an AE is treatment emergent, if an AE has a completely missing start and stop date, it will be considered treatment emergent; if the stop date is not missing, but the start date is completely missing, it will be considered treatment emergent unless the stop date occurs prior to the first dose of study drug.

For purpose of calculation of duration of AE, if a completely missing start and stop date occurs then it will be considered to have started on the date of first dose and stopped at the date of study termination. If stop date is present, and start date is completely missing, the start date will be imputed with the date of first dose of study drug unless the stop date occurs prior to first dose of study drug; in this case the start date will be imputed with the date of first dose of study drug. If start date is present and a completely missing stop date occurs, it will be considered to have stopped at the date of study termination for the patient.

For assessing treatment emergence or for calculation of duration of AE, if a partial start or stop date occurs, the following imputation process will be implemented:

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
Day missing, month and year present	• Month and/or year different to month and year of first study drug dose: Impute day with "01". • Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug.	Impute day with last day of the month
Day and month missing, year present	• Year different to year of first study drug dose: Impute day and month with "01JAN". • Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug.	Impute day and month with "31DEC"
Month missing, day and year present	• Year different to year of first study drug dose: Impute month with "JAN". • Year same as year of first study drug dose: Impute month with same month as first dose of study drug.	Impute with "DEC"
Caveats	• If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of AE.	

If the start date of any TEAE is incomplete or missing, the event will be assumed to be in the Induction Period, unless the incomplete start date (month and/or year) clearly indicates that the event started on or after the first dosing in Maintenance Period.

7.3.3. Prior/Concomitant Medications

For the purpose of assessing whether a medication is prior or concomitant, if a medication has a completely missing start date it will be considered a prior medication, and if a medication has a completely missing stop date it will be considered a concomitant medication. If a partial start or stop date occurs, the following imputation process will be implemented:

Partial Missing Start or Stop Date	Imputation for Start Date	Imputation for Stop Date
Day missing, month and year present	• Month and/or year different to month and year of first study drug dose: Impute day with "01" • Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug.	Impute day with last day of the month
Day and month missing, year present	• Year different to year of first study drug dose: Impute day and month with "01JAN" • Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug.	Impute day and month with "31DEC"
Month missing, day and year present	• Year different to year of first study drug dose: Impute month with "JAN" • Year same as year of first study drug dose: Impute month with same month as first dose of study drug.	Impute with "DEC"
Caveats	• If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of medication. • No stop date will be imputed if the treatment is ongoing.	

If the start date of any medication/procedure is incomplete or missing, and it is unclear when imputed whether the medication/procedure started in Induction or Maintenance Period, the medication/procedure will be assumed to be concomitant with both Induction and Maintenance Period, unless the incomplete start date (month and/or year) clearly indicates that the medication/procedure started on or after the first dosing in Maintenance Period.

7.4. Visit Windows

In general, all data from the eCRF will be organized and analyzed according to the scheduled time points. If the scheduled assessment is available, any additional or unscheduled assessments will not be used in the summary statistics per time point (unless otherwise discussed in the relevant section), but will be included in the data listings according to the date/time of assessment.

If the scheduled assessment is not available, the unscheduled assessment will be used if it is collected within from -6 to +7 days of the target day/timepoint for the scheduled assessment. If there are some unscheduled assessments available, the closest data to the Day will be used. If there are prior and post-Day data within same days from the Day, the later post-Day data will be used.

The unscheduled assessment could be available based on the following visit windows.

Scheduled assessment Visit - Week	Lower allowance	Target day	Upper allowance
Visit 3 - Week 2	8	14	21
Visit 4 - Week 4	22	28	35
Visit 5 - Week 6	36	42	49
Visit 6 - Week 8	50	56	63
Visit 7 - Week 10	64	70	77
Visit 8 - Week 12	78	84	91
Visit 9 - Week 14	92	98	105

7.5. Adjustments for Covariates

Unless otherwise specified, the statistical analysis models for the Induction Period efficacy and health outcome analysis will include the following stratification factors for Baseline randomization: age (adolescent patients 12 to <18 versus adults ≥18 years) and baseline disease severity (IGA=3 versus IGA=4). Additionally, the following factors will be included in the models:

- Country of patient as recorded at screening
- For analyses of the full population (i.e. not the subgroups of dupilumab naïve or previously exposed patients), the stratification factor of prior use of dupilumab (yes/no) will be included.

If the model does not converge, country will be removed as a factor from the specific model.

7.6. Subgroups

All endpoints will be analysed by previous exposure to dupilumab (Yes/No) as CCI .

For the maintenance phase, the analysis will be performed for both arms separately:

- Lebrikizumab (patients previously took lebrikizumab)
- Lebrikizumab (patients previously took placebo)

7.7. General Considerations for Efficacy during Induction Period

The Induction Period starts after the first injection of study treatment at Baseline Visit (Day 1) and ends prior to the first injection of study treatment at Week 16 or the early termination visit (ETV) (between Day 1 and Week 16). For patients who are randomized but not dosed, the Induction Period starts on the date of randomization.

For Pruritus Numeric Rating Scale (NRS) and Sleep-Loss due to Pruritus collected via eDiary, the baseline period is the 7-day window prior to the first injection. A patient must have responses on at least 4 of 7 days to calculate a baseline weekly mean. If a patient has 3 or fewer responses, the baseline mean value will be considered missing.

7.8. General Considerations for Efficacy during Maintenance Period

The Maintenance Period starts after the first injection of study treatment at Week 16 and ends after last injection of study treatment at Week 52.

Baseline for the Maintenance Period analyses will be the same as that for the Induction Period. See Section 7.2.4 for discussion on derivation of baseline.

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

7.9. Control for multiplicity

In the study there is no control for the overall type one error, only the primary endpoint needs to be statistically significant in order the study to be a success. Thus, no control for multiplicity approach is defined.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Patient Disposition and Withdrawals

The number of patients included in each analysis set will be summarised using descriptive statistics by study period and treatment group based on the Enrolled Subjects. The reasons for exclusion will be presented in the listings of protocol deviations, and in the Blind Data Review Meeting report In addition, patients completed treatment and discontinued, together with the reasons for discontinuation within each study period and follow-up will also be summarised by study period and treatment group based on FAS. Similarly, patients completed study and discontinued, together with the reasons for discontinuation will be summarized.

8.2. Protocol Deviations

Protocol deviations will be summarized descriptively for patients with at least 1 important protocol deviation and patients with at least 1 non-important protocol deviation for each treatment group and overall. Each protocol deviation will also be summarized descriptively within important and non-important protocol deviations for each treatment group and overall of the FAS. A patient can have multiple important and/or non-important deviations and counted once per important and/or non-important deviation. COVID-19-related protocol deviations will be summarized descriptively for each treatment group and overall of the FAS.

A listing of protocol deviations, including COVID-19-related protocol deviations, will be provided.

8.3. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be analysed by treatment group based on the FAS:

- Age (in years)
- Age group (Adolescents <=12 to <18 Years ; Adults >=18 Years)
- Sex (Male; Female)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Not Reported; Unknown)
- Race (White; Black or African American; American Indian or Alaska Native; Asian; Native Hawaiian or Other Pacific Islander; Other; Not Reported)
- Fitzpatrick Skin Type (I; II; III; IV; V; VI)
- Height (in cm)
- Weight (in kg)
- Body Mass Index (BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]
- Body Mass Index (BMI) categories (Underweight / normal weight/ overweight/ obesity)
- Prior use of dupilumab (Yes/No)
- Baseline disease severity: (IGA=3 / IGA=4)

- AD duration (based on AD onset, years)

8.4. Medical History and Concomitant Diseases

Medical history information, as recorded in eCRF, will be listed on the SAF.

Medical histories are defined as the conditions/events recorded on the *Medical History* electronic case report form (eCRF) with a start date prior to the first study drug injection.

The number and percentage of patients with medical histories will be summarized for the SAF Population by treatment group using the MedDRA Preferred Term (PT) nested within System Organ Class (SOC), MedDRA version 24.1 or higher.

8.5. Other Baseline Characteristics

Atopic Dermatitis History, Serology, Coagulation, and WOCBP as recorded on the eCRF will only be presented in data listings on the SAF.

8.6. Medication

Medications/procedures will be coded using the latest version of the WHODrug dictionary. The dictionary version used will be specified in the data display footnote. Imputation of missing and partial dates, for the purpose of assigning prior/concomitant status is described in Section 7.3.3.

8.6.1. Prior Medication

Medications/procedures that start prior to the date of first dose and stop prior to or on the date of first dose of study drug are considered prior medications/procedures. Prior medications will be summarized by treatment group and also presented in data listings on the SAF.

8.6.2. Concomitant Medication

Concomitant medications/procedures are those medications that start before, on, or after the first day of study treatment of the defined treatment period and continue into the treatment period. Concomitant medications are assigned to the treatment period in which they are actually ongoing. For example, if a patient is receiving a concomitant medication during the Induction Period but has a stop date during the Induction Period, the same medication would not be listed as a concomitant medication during the Maintenance Period unless patient has a new start date.

Patient incidence will be tabulated for the concomitant medications/procedures by Anatomic Therapeutic Class (ATC) and preferred term for all patients in the FAS, by treatment group and overall. Tables will be sorted by descending frequency of ATC level 2 and descending frequency of preferred term within the ATC level. Patients will be counted only once for each ATC and each preferred term in the event that they have multiple records of the same ATC or preferred term in the database. All concomitant medications/procedures will be presented in data listings.

8.6.3. Post Medication

Once the last dose of study drug is taken (i.e., the last visit at which the patient takes study drug) and related trial measurements are completed, 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 adverse events will be captured between the last study drug administration and last phone contact/visit (i.e., safety follow-up).

Post medications will be flagged in concomitant medication listings.

8.6.4. Rescue Medication

Rescue medications during the Induction Period and Maintenance Blinded Period will be presented by treatment group for the FAS Population. 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.

The use of rescue medications identified as an ICE will be summarized under the efficacy analyses of Section 9.3.

8.7. Extent of Exposure

Total drug exposure (in mg) is defined as the total investigational product in mg that was taken during the study.

Total exposure duration to investigational product (in days) is defined as: Date of last dose – date of first dose + 1. Note that this does not exclude days when the dose has been missed.

Percent of the planned exposure received is defined as the total drug exposure, divided by planned exposure, times 100.

For patients in the lebrikizumab arm,

- Patients who complete the Induction Period, planned exposure is 16 weeks of treatment planned, with a total dose equal to 2*500mg + 7*250 mg = 2750 mg
- Patients who complete the Maintenance Period, planned exposure is 35 weeks of treatment planned, with a total dose equal to 250 mg * 17 = 4250 mg
- German extension: total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose.

For patients in the placebo arm,

- Patients who complete the Induction Period, planned exposure is the loading dose at week 16, with a total dose equal to 2*250mg = 500 mg
- Patients who complete the Maintenance Period, planned exposure is 35 weeks of treatment planned, with a total dose equal to 2*250mg + 250 mg * 16 = 4500mg
- German extension: total dose (in mg) is calculated by the number of active injections taken during the treatment period multiplied by dose.

Finally, the total exposure in patient years will be calculated as:

$$Total\ exposure\ in\ patient\ years = \frac{Sum\ of\ duration\ of\ exposures\ for\ all\ patients\ in\ treatment\ group}{365.25}$$

Total drug exposure, total exposure duration, total exposure in patient years, and percent of the planned exposure received will be summarized using the SAF and actual treatment group for each period.

8.8. 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.

The formula to calculate the treatment compliance is the following:

$$Treatment\ compliance\ (\%) = 100 \times \frac{Total\ \mathbf{not\ returned}\ kit}{Total\ number\ of\ injections\ expected}$$

Where according to the eCRF entry instruction, the "Total not returned kits" is equivalent to the "total used kits".

Treatment compliance will be listed for each period.

9. Efficacy

9.1. Statistical Hypotheses

The statistical hypothesis to be tested for the main estimand of the primary efficacy endpoint (Percentage of patients achieving EASI 75 at Week 16) are:

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

where $P_{Lebrikizumab}$ refers to the true proportion of patients receiving lebrikizumab, and $P_{placebo}$ refers to the true 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 of the primary efficacy endpoint.

For analyses related to the Maintenance Period, only descriptive analyses will be presented. No specific statistical hypotheses thus apply for the Maintenance Period.

9.2. Definitions for Efficacy Endpoints

For all efficacy endpoints where a derived categorisation is defined in this section, if the category is collected on the eCRF then it will be used in the analysis and will not be derived. Otherwise, the category will be derived based on the recorded (or imputed) measure.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
Eczema Area and Severity Index (EASI)	The EASI scoring system uses a defined process (Steps 1-5 below) to grade the severity of the signs of eczema and the extent affected. The extent of disease (percentage of skin affected: 0 = 0%; 1 = 1-9%; 2 = 10-29%; 3 = 30-49%; 4 = 50-69%; 5 = 70-89%; 6 = 90-100%) and the severity of 4 clinical signs (erythema, edema/papulation, excoriation, and lichenification) each on a scale of 0 to 3 (0 = none, absent; 1 = mild; 2 = moderate; 3 = severe) at 4 body sites (head and neck, trunk, upper limbs, and lower limbs). Half scores are allowed between severities 1, 2 and 3. Each body site will have a score that ranges from 0 to 72, and the final EASI score will be obtained by weight-averaging these 4 scores. Hence, the final EASI score will range from 0 to 72 for each time point.	EASI score	Derive EASI region score for each of head and neck, trunk, upper limbs, and lower limbs as follows: $EASI_{region}$ = (Erythema + edema/papulation + Excoriation + Lichenification) *(value from percentage involvement), where erythema, edema/papulation, excoriation, and lichenification are evaluated on a scale of 0 to 3 and value from percentage involvement is on a scale of 0 to 6. Then total EASI score is as follows: EASI = $0.1*EASI_{head\ and\ neck}$ + $0.3*EASI_{trunk}$ + $0.2*EASI_{upper\ limbs}$ + $0.4*EASI_{lower\ limbs}$	If value of percentage involvement is 0 for any region, then severity scores of that region could be missing. Otherwise missing if any component is missing.
		EASI 50	% Improvement in EASI score from baseline ≥ 50%: % change from baseline ≤-50	Missing if baseline or observed value is missing.
		EASI 75	% Improvement in EASI score from baseline ≥75%: % change from baseline ≤-75	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
		EASI 90	% Improvement in EASI score from baseline ≥90%: % change from baseline ≤-90	Missing if baseline or observed value is missing.
		Time (in days) to EASI 50 (75) (90) up to week 16	Date of first time % change from baseline in EASI score ≥-50 (75) (90) - date of W16 visit +1	If a patient has not experienced achievement of EASI 50 (75) (90) by completion or early discontinuation of Induction Period, the patient will be censored at the date of their last visit during Induction Period.
		Time (in days) to EASI 50 (75) (90) between week 16 and week 52	Date of first time % change from W16 visit in EASI score ≥-50 (75) (90) - date of W52 visit +1	If a patient has not experienced achievement of EASI 50 (75) (90) by completion or early discontinuation of Maintenance Period, the patient will be censored at the date of their last visit during Maintenance Period.
Investigator's Global Assessment (IGA)	The IGA is a static assessment and rates the severity of the patient's AD. The IGA is comprised of a 5-point scale ranging from 0 (clear) to 4 (severe) and a	IGA score	Single item. Range: 0 to 4 0 represents "clear" 4 represents "severe"	Single item, missing if missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
	score is selected using descriptors that best describe the overall appearance of the lesions at a given time point.	IGA 0/1 with 2-point improvement	Observed score of 0 or 1 and change from baseline = -2	Missing if baseline or observed value is missing. Single item, missing if missing.
Body Surface Area (BSA)	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% rule	BSA score	BSA Total = $BSA_{head\ and\ neck}$ + BSA_{trunk} + $BSA_{upper\ extremities}$ + $BSA_{lower\ extremities}$	N/A – partial assessments cannot be saved.
		Change from baseline in BSA score	Change from baseline: observed BSA score – baseline BSA score	Missing if baseline or observed value is missing.
SCORing Atopic Dermatitis (SCORAD)		SCORAD score	SCORAD = A/5 + 7B/2 + C, where A is extent of disease, range 0-100 B is disease severity, range 0-18 C is subjective symptoms, range 0-20	Missing if component A or B or C is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
	SCORAD is a validated clinical tool for assessing the extent and intensity of atopic dermatitis. There are 3 components to the assessment: • The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). • The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and of sleeplessness is recorded for each symptom by the patient or relative on a VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20 (assigned as "C" in the overall SCORAD calculation.	Change from baseline in SCORAD score	Change from baseline: observed SCORAD score – baseline SCORAD score	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
Pruritus Numeric Rating Scale (NRS)	The Pruritus Numeric Rating Scale (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." Assessments will be recorded daily by the patient using an electronic diary.	Pruritus NRS prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If the patient has at least one daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0-10.	Weekly mean score missing if the patient has no Pruritus-NRS responses within the week.
		4-point Pruritus improvement in Pruritus NRS prorated weekly mean score	Change from baseline in Pruritus NRS prorated weekly mean score ≤-4	Missing if baseline is missing or observed value is missing.
Sleep-loss	Sleep-loss due to pruritus will be assessed by the patient. Patients rate their sleep based on a 5-point Likert scale [0 (not at all) to 4 (unable to sleep at all)]. Assessments will be recorded daily by the patient using an electronic diary.	Sleep-loss prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If the patient has at least one daily score within the week, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0 to 4.	Weekly mean score missing if the patient has no Sleep-loss responses within the week.
		Change from baseline in Sleep-loss prorated weekly mean score	Change from baseline: observed sleep loss prorated weekly mean score – baseline sleep loss score	Missing if baseline or observed value is missing.
Skin Pain NRS	The Skin Pain NRS is an 11-point scale used by patients to rate their worst pain over the past 24 hours with 0 indicating "No pain" and 10 indicating "Worst pain imaginable." Assessments will be recorded daily by the patient using an electronic diary.	Skin Pain NRS prorated weekly mean score	The prorated weekly mean is based on previous 7 days. If the patient has at least one daily score, the weekly mean is the prorated average of daily scores within the given week. Single item; range 0-10.	Weekly mean score missing if the patient has no Skin Pain NRS responses within the week

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
		Change from baseline	Change from baseline: observed Skin Pain NRS prorated weekly mean score – baseline Skin Pain NRS score	Missing if baseline or observed value is missing.
		4-point Skin Pain NRS improvement	Change from baseline in Skin Pain NRS prorated weekly mean score ≤-4	Missing if baseline or observed value is missing.
Patient-Oriented Eczema Measure (POEM)	The POEM is a 7-item, validated, questionnaire used by the patient to assess disease symptoms over the last week. The patient is asked to respond to 7 questions on skin dryness, itching, flaking, cracking, sleep loss, bleeding and weeping. All 7 answers carry equal weight with a total possible score from 0 to 28 (answers scored as: No days=0; 1– 2 days = 1; 3-4 days = 2; 5–6 days = 3; everyday = 4). A high score is indicative of a poor quality of life. POEM responses will be captured using an electronic diary and transferred into the clinical database.	POEM score	POEM total score: sum of questions 1 to 7, Range 0 to 28.	If a single question is left unanswered, then that question is scored as 0. If more than one question is unanswered, then the tool is not scored. If more than one response is selected, then the response with the highest score is used.
		Change from baseline in POEM score	Change from baseline: observed POEM score – baseline POEM score	Missing if baseline or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
Dermatology Life Quality Index (DLQI)	DLQI is a validated, dermatology-specific, patient-reported measure that evaluates patient's health-related QoL. This questionnaire has 10 items that are grouped in 6 domains, including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period of this scale is over the "last week". Response categories and corresponding scores are: Very much = 3 A lot = 2 A little = 1 Not at all = 0 Not relevant = 0 Scores range from 0-30 with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related QoL (Hongbo et al. 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji et al. 2002; Basra et al. 2008)	DLQI total score	A DLQI total score is calculated by summing all 10 question responses and has a range of 0-30 (less to more impairment)	Score of 1 unanswered question = 0; If 2 or more questions are missing, the total score is missing. Note: #7B could be a valid missing while #7A is not "No." That is, #7 should be considered as 1 question.
		4-point improvement	Change from baseline ≤-4	Missing if baseline is missing or observed value is missing.
		DLQI total score and domain scores change from baseline	Calculated for each post-baseline assessment as: observed DLQI (total score or domain scores) – baseline DLQI (total score or domain scores)	Missing if baseline or observed value is missing
Children's Dermatology Life Quality Index (CDLQI)	The CDLQI is designed to measure the impact of any skin disease on the lives of children. Patients ≤16 years will complete the CDLQI and should continue to complete the CDLQI for the duration of the study. The scoring of each question is:	CDLQI total score	A CDLQI total score is calculated by summing all 10 question responses and has a range of 0-30	Score of 1 unanswered question = 0; If 2 or more questions are missing, the total score is missing.
		4-point improvement	Change from baseline ≤-4	Missing if baseline is missing or observed value is missing.

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
	• Very much = 3 • Quite a lot = 2 • Only a little = 1 • Not at all = 0 • Question unanswered = 0 • Question 7: 'Prevented school' (text-only questionnaire) = 3	CDLQI total score and domain scores change from baseline	Calculated for each post-baseline assessment as: observed CDLQI (total score or domain scores) – baseline CDLQI (total score or domain scores)	Missing if baseline or observed value is missing
Dermatology Life Quality Index-Relevant (DLQI-R)	The DLQI-Relevant (DLQI-R) is a recently developed scoring that adjusts the total score of the questionnaire for the number of 'not relevant' responses (NRRs) indicated by a patient.	Change from Baseline in DLQI-R total score by week up to Week 16	The DLQI-R total score is calculated by summing the score of the 10 items. From here, the DLQI-R total score is calculated for each patient at each visit as the total DLQI score multiplied by 10/(10-NRR), where NRR is the number of not relevant responses for questions 3-10. Change calculated for each post-baseline assessment as: observed DLQI-R total score – baseline DLQI-R total score	Missing if baseline is missing or observed value is missing.
Topical Corticosteroids (TCS)	Topical Corticosteroids (TCS) Diary records patient's treatment of Atopic Dermitatitis with a TCS and the areas of application. Assessments will be recorded daily up to W2, weekly from W2 to W16, and every 4 weeks from W16 onward by the patient using an electronic diary.	Proportion of free days from baseline to week 16	Proportion of TCS-free days is calculated as the total number of days in study from baseline to Week 16 where TCS were not used, divided by the total number of days in study from baseline to Week 16.	If patient does not complete study until Week 16 then total number of days will be capped at the date of the last assessment in study

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
		Time to TCS-free days from baseline to week 16	Time to TCS-free days is calculated as the time from baseline to first point where TCS are not used or Week 16 + 1, whichever is the earlier.	If patient does not complete study to Week 16 then censor at the date of the last assessment in study
RECAP	RECAP is a seven-item questionnaire designed to capture the experience of eczema control in all ages and eczema severities. Each of the seven questions in RECAP carries equal weight and is scored from 0 to 4 (total score of 0-28).	Change from Baseline in RECAP by week up to Week 16	The total RECAP score is calculated as the sum of all question scores. Change calculated for each post-baseline assessment as: observed RECAP total score – baseline RECAP total score	If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28. If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are selected, the response option with the highest score should be recorded
World Health Organisation – Five Well-Being Index (WHO-5)	The WHO-5 is a short, self-administered measure of well-being over the last two weeks. It consists of five positively worded items that are rated on 6-point Likert scale, ranging from 0 (at no the time) to 5 (all of the time). The raw scores are transformed to a score from 0 to 100, with lower scores indicating worse well-being. A score of ≤50 indicates poor wellbeing and suggests further investigation into possible symptoms of depression. A score of 28 or below is indicative of depression.	Change from Baseline WHO-5 by week up to Week 16	Total raw score calculated as the sum of all raw scores. The total raw score (ranging from 0 to 25) is then multiplied by 4 to get the transformed total score between 0 and 100. Change calculated for each post-baseline assessment as: observed WHO-5 transformed total score – baseline WHO-5 transformed total score	None

Measure	Description	Variable	Derivation / Comment	Imputation Approach if Missing Components
Treatment Satisfaction Questionnaire for Medication-9 items (TSQM-9)	Version 9 of the TSQM consists of 9 items that results in three specific domains: Effectiveness, Convenience, and one global scale item, Global Satisfaction. Scores for each domain are computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100.	EFFECTIVENESS	([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100	If one item is missing ([(Sum(Item 1? + Item 2? + Item 3?)) – 2] divided by 12) * 100
		CONVENIENCE	([Sum(Item 9 to Item 11) – 3] divided by 18) * 100	If one item is missing ([(Sum(Item9? to Item11?)) – 2] divided by 12) * 100
		GLOBAL SATISFACTION	([Sum(Item 12 to Item 14) – 3] divided by 14) * 100	If either Item 12 or 13 is missing ([(Sum(Item12? to Item14?)) – 2] divided by 10) * 100 If Item 14 is missing ([(Sum(Item12 and Item13)) – 2] divided by 8) * 100

Abbreviations: eCOA = electronic clinical outcome assessment

9.3. Analysis of the Primary and Key Secondary Efficacy Endpoints

The primary and key secondary efficacy 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). 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) 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. The primary analysis will be based on the 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.

Details are described in Appendix 2. Details of Combining Estimates and Test Statistics for Categorical Endpoints with Multiple Imputation

Example code for CMH test:

CCI

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).

SAS Proc MIANALYZE will be used to combine the 100 point estimates (main estimand) for the difference in percentage of patients achieving EASI 75 response at Week 16 between treatments and standard errors, allowing appropriate statistical inference as described below:

CCI

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:

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.

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.

In addition, to support efficacy analyses, a summary of the incidence of the ICEs at each visit up to Week 16 will be presented.

9.4. Analysis of all Other Secondary and Other Efficacy Endpoint

The main and second estimands as described in Section 6.1.2 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.

Example SAS syntax is as follows:

CCI

CCI

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

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

Additionally, all secondary and CCI efficacy endpoints for the secondary objective will be presented in by-patient listings.

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

The same analyses described for the Primary efficacy analyses (Section 9.3) will be performed by previous exposure to dupilumab (Yes/No), 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.

9.6. Summary of the Statistical Efficacy Analysis to be performed with Induction period data

The table below provides the detailed analyses relative to estimands including analysis type, method and imputation, population, time point, and treatment comparisons for efficacy/health outcomes analyses.

Measure	Variable	Estimand (Section 6)	Analysis Method (Section 6.3)	Population (Section 5)	Analysis Type
Eczema Area and Severity Index (EASI)	Proportion of patients achieving EASI 75 at W16	Primary Estimand (Hybrid)	CMH analysis with MCMC-MI	FAS PPS	Primary analysis: EASI 75 at W16 Key secondary analysis: EASI 90 at W16 EASI 75; 90 and 50 up to W16
		Supportive Estimand (Hypothetical)	NRI	FAS	Primary analysis: EASI 75 at W16 Key secondary analysis: EASI 90 at W16 EASI 75; 90 and 50 up to W16
	Time to EASI 75	NA	NA	FAS	CCI analysis: time to EASI 50-75-90 up to W16
Investigator's Global Assessment (IGA)	Proportion of patients achieving IGA [0,1] with a ≥2-point improvement at W16	Primary Estimand (Hybrid)	MCMC-MI	FAS PPS	Key secondary analysis: achieving IGA [0,1] with a ≥2-point improvement at W16

Measure	Variable	Estimand (Section 6)	Analysis Method (Section 6.3)	Population (Section 5)	Analysis Type
		Supportive Estimand (Hypothetical)	NRI	FAS	Key secondary analysis: achieving IGA [0,1] with a ≥2-point improvement at W16
Pruritus NRS	Proportion of patients achieving at least 4-point improvement in pruritus NRS at W16	Primary Estimand (Hybrid)	MCMC-MI	FAS* PPS*	Key secondary analysis: achieving at least 4-point improvement in pruritus NRS at W16
		Supportive Estimand (Hypothetical)	NRI	FAS*	Key secondary analysis: achieving at least 4-point improvement in pruritus NRS at W16
	Change from baseline in Pruritus NRS up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Change from baseline in Pruritus NRS up to W16
Body Surface Area (BSA)	Change from baseline in BSA score up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Change from baseline in BSA score up to W16

Measure	Variable	Estimand (Section 6)	Analysis Method (Section 6.3)	Population (Section 5)	Analysis Type
SCORing Atopic Dermatitis (SCORAD)	Change from baseline in SCORAD score up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Change from baseline in SCORAD score up to W16
Sleep-loss Score	Change from baseline sleep loss up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Change from baseline sleep loss up to W16
Patient-Oriented Eczema Measure (POEM)	Change from baseline in POEM score	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Change from baseline POEM up to W16
(Children) Dermatology Life Quality Index (DLQI/ CDLQI)	Change from baseline in DLQI total score up to W16 Change from baseline in CDLQI total score up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Change from baseline DLQI/ CDLQI up to W16
	Proportion of patients achieving at least 4-point improvement in DLQI up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS*	Key secondary analysis: achieving at least 4-point improvement in DLQI up to W16

Measure	Variable	Estimand (Section 6)	Analysis Method (Section 6.3)	Population (Section 5)	Analysis Type
Topical corticosteroids (TCS)-free TCS data collected in CRF and not from eDiary.	Proportion of TCS-free days up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Proportion of TCS-free days up to W16
	Time to TCS-free days up to W16	Primary Estimand (Hybrid)	Kaplan-Meier	FAS	Key secondary analysis: Time to TCS-free days up to W16
	Time to TCS-free days up to W16	Secondary Estimand (Composite)	Kaplan-Meier	FAS	Key secondary analysis: Time to TCS-free days up to W16
Skin Pain NRS	Change from baseline Skin Pain NRS up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	Key secondary analysis: Change from baseline Skin Pain NRS up to W16
	Percentage of patients achieving a 4-point improvement Skin Pain NRS at W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS*	Key secondary analysis: Percentage of patients achieving a 4-point improvement Skin Pain NRS at W16
Recap of atopic eczema (RECAP)	Change from Baseline RECAP up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	CCI analysis: Change from Baseline RECAP up to W16

Measure	Variable	Estimand (Section 6)	Analysis Method (Section 6.3)	Population (Section 5)	Analysis Type
World Health Organisation – Five Well-Being Index (WHO-5)	Change from Baseline WHO-5 up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	CCI analysis: Change from Baseline WHO-5 up to W16
Treatment Satisfaction Questionnaire for Medication-9 items (TSQM-9)	TSQM-9 up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	CCI analysis: TSQM-9 up to W16
DLQI-Relevant (DLQI-R)	Change from Baseline DLQI-R up to W16	Primary Estimand (Hybrid)	MMRM and BOCF	FAS	CCI analysis: Change from Baseline DLQI-R up to W16

** The analyses of 4point NRS pruritus improvement will be based on those patients that had a baseline NRS pruritus score ≥ 4points*
The analyses of 4point DLQI improvement will be based on those patients that had a baseline DLQI score ≥ 4points
The analyses of 4point NRS SKIN Pain improvement will be based on those patients that had a baseline NRS SKIN Pain score ≥ 4points.

9.7. Maintenance Period (and Extension Period for Patients from Germany) Analyses

The Induction and Maintenance/Extension Periods will be reported separately. For the Maintenance/Extension Period, the same analyses as for Induction Period, as described in section エラー! 参照元が見つかりません。, will be performed descriptively on the FAS.

10. Safety

The population used for safety analyses will be the Safety Analysis Set (SAF). Safety will be assessed based on adverse event (AE), treatment emergent adverse event (TEAE), vital signs, laboratory results, and physical examinations.

Safety will be described by treatment groups:

- Up to Week 16: Lebri / Placebo
- Up to Week 52/68/Extension period: Lebri-Lebri / Placebo-Lebri

All safety analysis except for laboratory evaluations/vital signs/physical examinations will be summarized for the three study periods described below:

- Induction Period (up to Week 16),
- Maintenance Period and Safety Follow-up:
    - For all patients: from Week 16 to Week 52
    - For all patients except German patients in the extension: from Week 16 to 68
    - For German patients in the extension: from Week 16 to last visit in the German extension
- Combined Induction and Maintenance/Extension Periods (up to Week 52 or later for the Extension as described above – see maintenance period), and Combined Induction and Maintenance/Extension Periods plus Follow-Up Period [selective analysis] (Up to Week 68 or later for the Extension as described above – see maintenance period).

10.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA Version 24.1 or higher. In the event of a missing/incomplete start or stop date associated with an adverse event, only the treatment-emergence will be imputed using the algorithm described in エラー! 参照元が見つかりません。 section 7.3.2. Dates will not be imputed.

A TEAE is any AE that newly appeared, or worsened in severity following initiation of study medication until last follow-up visit. Only TEAE will be included in the summary tables, but all AE will be included in the listings.

Following tables will be produced:

- An overall summary of the number and percentage of patients reporting TEAEs, Adverse Events of Special Interest (AESI), serious TEAEs, Suspected Unexpected Serious Adverse Reactions (SUSARs), TEAEs leading to study drug discontinuation, related TEAEs, related SAEs and Deaths.
- Incidence of AEs (AEs including TEAEs, SAEs, related TEAEs, related SAEs, TEAEs leading to study treatment discontinuation, AESIs and deaths)
- TEAEs overall and by system organ class and preferred term

- TEAEs by severity (Mild, Moderate, Severe), overall and by system organ class and preferred term
- TEAEs by relationship to study treatment (unrelated vs. related), overall and by system organ class and preferred term
- TEAEs leading to study drug discontinuation, overall and by system organ class and preferred term
- TEAEs leading to death, overall and by system organ class and preferred term
- Serious Adverse Events, overall and by system organ class and preferred term
- AESIs by severity (Mild, Moderate, Severe), overall and by preferred term
- AESIs by relationship to study treatment (unrelated vs. related), overall and by preferred term
- SUSARs, overall and by system organ class and preferred term

AEs possibly related and related to study medication will be combined for the "related" summaries.

If a patient met the same AE more than one time, AE will be counted only once with the maximum of severity.

10.2. Laboratory Evaluations

All statistical analyses of laboratory values will be performed using SI units.

Clinical laboratory data and change from baseline will be summarized by the scheduled time point for the serum chemistry, hematology and urinalysis to weeks 16, 32 and 52 plus German extension weeks.

Patient incidences of change in classification with respect to the laboratory normal ranges will be summarized as shift tables.

Shift tables will show the number of patients who shift from each category of maximum (minimum) baseline observation to each category of maximum (minimum) post-baseline observation. Here categories may be low, normal, or high according to the central lab definition.

Baseline will be the last value obtained before randomization.

Chemistry and hematology data will be listed with the values outside the normal ranges flagged.

10.3. Vital Signs

Summary statistics for vital sign (systolic and diastolic blood pressure [mmHg], body temperature [°C], respiratory rate [breaths per minute] and pulse [beats per minute or bpm]) will be presented for each scheduled time point measured and for the change from baseline to each time point.

For convenience, the conversion for temperature:

Temperature (in °C) = 5/9 (Temperature [in °F]-32)

Observed results and changes from baseline to weeks 2, 4, 8, 12 and 16 will be summarized.

Observed results and changes from baseline to weeks 20, 24, 28, 32, 36, 40, 44, 48 and 52 plus German extension weeks will be summarized.

Number and percentage of patients who shift from normal/high to low (ie, treatment-emergent low) and the number and percentage of patients who shift from normal/low to high (ie, treatment-emergent high) will be displayed.

Table of Categorical Criteria for Abnormal Treatment -Emergent Blood Pressure and Pulse measurement, and Categorical Criteria for Weight Changes for Adult

Parameter	Low	High
Systolic BP (mmHG)	≤90 and decrease from baseline ≥20	≥140 and increase from baseline ≥20
Diastolic BP (mmHG)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm)	≤50 and decrease from baseline ≥15	≥100 and increase from baseline ≥15
Weight (kg)	(Loss) decrease ≥7%	(Gain) increase ≥7%

10.4. Physical Examination

Clinically significant physical examination abnormalities will be summarized at weeks 16, 32 and 52 plus German extension weeks.

Results of physical examination will be listed by patient and visit.

10.5. Special Safety Topics including Adverse Events of Special Interest

10.5.1. Eosinophilia and Eosinophil-Related Disorders

In addition to the standard laboratory analysis (Section 10.2), eosinophilia and eosinophil-related AEs will be summarized for the SAF. Details regarding eosinophil-related PTs are described in the separate Almirall Safety Topics of Interest.

A shift table summarizing the number and percentage of patients within each maximum baseline category versus each maximum post-baseline category by treatment will be displayed for the SAF. The following Eosinophil categories will be considered:
Eosinophil categories: normal (<500 per microliter), mild (500 to <1500 per microliter), moderate (1500 to <5000 per microliter), severe (>=5000 per microliter).

10.5.2. Infections, Including Herpes Infections and Relevant Parasitic Infections

Infections will be defined using the PTs from the MedDRA Infections and Infestations SOC. The MedDRA terms used to identify infections considered to be opportunistic infections (OI) in patients with immune mediated inflammatory conditions treated with immunomodulatory drugs are based on Winthrop et al. (2015) and are listed in the Almirall Safety Topics of Interest. The list contains narrow (more specific) and broad (less specific) PTs with respect to these prospectively defined OIs. Definitions of herpes infections, parasitic infections and skin infections are listed in the Almirall Safety Topics of Interest.

The following tables will be produced for the SAF:

- Summary of treatment-emergent infections by PT by maximum severity
- Summary of serious infections by PT
- Summary of infection AEs resulting in permanent study drug discontinuation
- Treatment-emergent potential OI by PT nested with categories for narrow terms and broad terms separately
- Treatment-emergent adverse events, herpes and parasitic infections
- Treatment-emergent adverse events, skin infection

In addition, a listing of patients with potential OI, Serious Infection, herpes and parasitic infections will be displayed.

10.5.3. Conjunctivitis

Conjunctivitis are events of special interest and will be identified using PTs nested within the categories of conjunctivitis and Keratitis as described in the Almirall Safety Topics of Interest:

The following tables and listings will be produced for the SAF:

- Summary of TEAE of conjunctivitis overall and by categories, and also describing severity, seriousness, outcome and action taken.
- Summary and/or listing of conjunctivitis and eye inflammation follow-up form
- A listing of patients with conjunctivitis

10.5.4. Hypersensitivity

Potential hypersensitivity reactions will be determined using the following Standardised MedDRA Query (SMQs): anaphylactic reaction, hypersensitivity, and angioedema. Potential hypersensitivity will be categorized as immediate (i.e., occurring the same day as drug administration) and non-immediate (i.e., occurring after the day of study drug administration but prior to subsequent drug administration).

- for immediate hypersensitivity: (1) combined narrow/algorithmic search (that is, any narrow term from any one of the SMQs, or anaphylaxis algorithm); (2) narrow search (that is, any narrow term) by SMQ; (3) TEAEs (occurring on the day of study drug administration) by PT not in any of the 3 SMQs

- for nonimmediate hypersensitivity: (1) combined narrow search (that is, any narrow term from any one of the SMQs); (2) narrow search (that is, any narrow term) by SMQ; and (3) broad search (that is, any narrow or broad term) by SMQ

10.5.5. Injection Site Reactions (ISR)

Injection site reactions (ISRs) are AEs localized to the immediate site of the administration of a drug. The evaluation of study drug related ISRs will be through the unsolicited reporting of ISR TEAEs. Injection site reactions will be defined using the MedDRA High Level Term (HLT) of ISR, excluding certain PTs related to joints as described in the Almirall Safety Topics of Interest.

A summary table of TEAE of ISR overall and by PT will be displayed.

10.5.6. Malignancies

Malignancies will be defined using PTs from the Malignant tumors SMQ and summarized separately for the 2 categories: Non-melanoma skin cancer (NMSC) and Malignancies excluding NMSC.

10.5.7. Atopic Dermatitis Exacerbation

A summary table of TEAE of atopic dermatitis exacerbation will be displayed. Atopic dermatitis exacerbation will be defined using the following PTs:

- Dermatitis atopic
- Eczema
- Rebound atopic dermatitis
- Rebound eczema
- Dermatitis allergic
- Erythrodermic atopic dermatitis

11. Changes from Analysis Planned in Protocol

The reasons for exclusion will be presented in the listings of protocol deviations instead of summarizing in table.

Any analysis described as 'by visit' in the protocol are described as 'by week' in this SAP and in the tables and figures.

Following 2 Secondary Endpoints are added in this SAP.

- Percentage of patients achieving IGA 0/1 and 2-point improvement by week up to Week 16.
- Percentage of patients achieving a 4-point improvement Pruritus NRS by week up to Week 16.

12. Reference List

[1] Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh). 1980;92(suppl):44-47

[2] Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397. doi:10.1016/j.jaci.2005.12.1303

13. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output
- One output file can contain several outputs.or each output will be stored in a separate file
- Output files will be delivered in Word format or portable document format pdf
- Numbering of TFLs will follow ICH E3 guidance

13.2. Table, Figure, and Listing Format

13.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output will have the following header at the top left of each page:
- ALMIRALL S.A. Protocol M-17923-30 ADvantage PPD Health study number CCI)

- Draft/Final Run
- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page

13.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Full Analysis Set)

13.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment
- For numeric variables, include 'unit' in column or row heading when appropriate
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable)

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;

- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters,all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more patients
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the

highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'

- The percentage of patients will normally be calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of patients exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of patients) where a patient can be included in more than one category, a footnote or programming note will be added describing whether the patient is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, patient number, visit/collection day, and visit/collection time

- Missing data will be represented on patient listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on patient listings as dashes (–JUL2000). Dates that are missing because they are not applicable for the patient will be output as 'N/A', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study

- Units will be included where available

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display

- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible
- Patient specific footnotes are avoided, where possible
- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when mutiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in PPD Developing Statistical Programs SOP (3907) .

PPD Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

15. Appendices

Appendix 1. Study Visit Mapping for Pruritus NRS and Sleep-loss Diary and POEM

Pruritus NRS and sleep loss are collected as a daily diary; entries will be mapped to study week by the following:

Week	Start Day	End Day
Baseline	Date of First Injection[a] - 7	Date of First Injection-1
Week 2	Week 2 Visit Date – 7	Week 2 Visit Date - 1
Week 4	Week 4 Visit Date – 7	Week 4 Visit Date – 1
Week 6	Week 6 Visit Date – 7	Week 6 Visit Date - 1
Week 8	Week 8 Visit Date – 7	Week 8 Visit Date - 1
Week 10	Week 10 Visit Date – 7	Week 10 Visit Date - 1
Week 12	Week 12 Visit Date – 7	Week 12 Visit Date – 1
Week 14	Week 14 Visit Date – 7	Week 14 Visit Date - 1
Week 16	Week 16 Visit Date – 7	Week 16 Visit Date – 1
Week 20	Week 20 Visit Date – 7	Week 20 Visit Date – 1
Week 24	Week 24 Visit Date – 7	Week 24 Visit Date – 1
Week 28	Week 28 Visit Date – 7	Week 28 Visit Date – 1
Week 32	Week 32 Visit Date – 7	Week 32 Visit Date – 1
Week 36	Week 36 Visit Date – 7	Week 36 Visit Date – 1
Week 40	Week 40 Visit Date – 7	Week 40 Visit Date – 1
Week 44	Week 44 Visit Date – 7	Week 44 Visit Date – 1
Week 48	Week 48 Visit Date – 7	Week 48 Visit Date – 1
Week 52	Week 52 Visit Date – 7	Week 52 Visit Date – 1

[a] If date of first injection is missing, the randomization date will be used.

If multiple assessments on a single day are present, use the first assessment. If an assessment could be mapped to different weeks, it will be mapped to the earlier week. Derivation of the weekly mean

scores for Pruritus NRS and Sleep-loss could be found in the table in the section 9.2. Definitions for Efficacy Endpoints. If at least 1 of the 7 days contains non-missing daily assessments, post-baseline weekly score will be calculated using prorated weekly average. If the range of 7 days are all missing daily assessments, then the weekly score is missing.

POEM are collected every week via eDiary, the visit week mapping will follow the following rule: the last collected POEM data before the visit date would be used, the evaluation window is injection date - 7 to injection date –1 for baseline and assessment date - 7 to assessment date –1 for post-baseline. For example, if a patient gets an injection/assessment on the 14th, we would use the scale completed in between the 13th and the 7th.

Appendix 2. Details of Combining Estimates and Test Statistics for Categorical Endpoints with Multiple Imputation

Following the implementation of MCMC-MI imputation as specified in Section エラー! 参照元が見つかりません。, the data sets with imputations should be set together and sorted by imputation number. The following sections describe the processes for combining inferences for the individual imputed data sets into one inference for reporting. All calculations are performed in SAS software version 9.4 or higher.

Summarize Unadjusted Response Rate

The response rates, overall and by treatment arm, and their associated standard errors (SE) are computed for each imputed data set using PROC FREQ with the *riskdiff* option specified for the appropriate column in the TABLES statement. The response rates and SEs from the resulting output are combined across the imputed data sets using PROC MIANALYZE, separately for each arm and the overall group.

Note that the estimate and 95% confidence interval (CI) bounds output by PROC MIANALYZE are percents (i.e., they are in terms of the response rate). To obtain the number of responders, the estimated percentage is multiplied by the number of individuals in the analysis population and rounded to the nearest integer.

Compute Stratified Measures of Association

The common risk difference, common odds ratio (OR), and Cochran-Mantel-Haenszel (CMH) test statistic are computed for each imputed data set using PROC FREQ with the *riskdiff* option for the appropriate column (for risk difference) and the *cmh* option (for odds ratio and CMH test statistic) specified in the TABLES statement. Each of these analyses are stratified by geographic region, age group, and baseline disease severity via inclusion of these variables in the TABLES statement with the treatment and outcome variables.

Note that the PROC FREQ output corresponding to the Mantel-Haenszel method is used for the risk difference, and the output corresponding to the General Association statistic is used for the CMH statistic. PROC MIANALYZE is then called separately for each of these measures, with further details in the sections below.

Common Risk Difference

No transformation is necessary before using PROC MIANALYZE to combine the risk difference estimates and their associated SEs across the imputed data sets. This procedure outputs an estimate of the common risk difference and the associated 95% CI bounds.

Common Odds Ratio

The OR from each imputed data set is first transformed using the natural logarithm. The SE for each log OR (SE_{lOR}) is derived from the OR 95% CI bounds (LB_{OR}, UB_{OR}) according to the following equation: $SE_{lOR} = (\ln(UB_{OR}) - \ln(LB_{OR}))/(2 * 1.96)$. The log OR and derived SE are then combined using PROC MIANALYZE, which outputs a combined estimate of the log OR and the associated 95% CI. Finally, these measures can be exponentiated to transform them back to the OR scale.

Cochran-Mantel-Haenszel Test

The CMH test statistic (CMH) from each imputed data set is transformed using the Wilson-Hilferty transformation and standardized so that it has approximately a standard Normal distribution (Ratitch 2013). In particular, the transformed CMH statistic is computed as follows: $CMH_{WH} = \frac{(\frac{CMH}{df})^{\frac{1}{3}} - (1 - \frac{2}{9*df})}{\sqrt{\frac{2}{9*df}}}$, where df is the degrees of freedom of the CMH statistic. Then the SE for each CMH_{WH} is 1, and PROC MIANALYZE is used to output a combined estimate of the transformed CMH statistic. Note that the two-sided p-value output by PROC MIANALYZE is not used directly, but instead the one-sided p-value is computed manually using both the t statistic and two-sided p-value output by PROC MIANALYZE: if t statistic is greater than 0, then one-sided p-value is computed as half of the two-sided p-value; otherwise, the one-sided p-value is computed as 1 - half of the two-sided p-value. The resulting one-side p-value is reported as the pooled p-value for the CMH test.

Appendix 3. Definition of Rescue Medications

This appendix provides the definition of rescue medications for this study, including topical and systemic treatments defined as follows:

1. **Topical Atopic Dermatitis Treatment (including topical corticosteroids, TCI, and crisaborole)**

Route of topical treatments includes: Topical and Transdermal.

Topical Corticosteroids (TCS): ATC code is D07

High or Ultra High Potency TCS: as per eCRF classification

Topical calcineurin inhibitor (TCI): Preferred Term includes: TACROLIMUS, PIMECROLIMUS

Crisaborole: Preferred Term includes: CRISABOROLE

2. **Systemic Atopic Dermatitis Treatment (including systemic corticosteroids, immunosuppressant, biologics and phototherapy/photochemotherapy)**

Route of systemic treatments administration includes: Oral, Intra-Arterial, Intramuscular, Intraperitoneal, Intravenous, Subcutaneous, Transdermal. (This condition applies to the following categories except for phototherapies.)

Systemic Corticosteroids: ATC code is H02

Immunosuppressant: Defined as: ATC2 is L04 or Preferred terms of Abrocitinib or Ruxolitinib or Upadacitinib or Baricitinib

Biologics: Defined as following Preferred terms:

Infliximab, Infliximabum, Etanercept, Etanerceptum, Adalimumab, Adalimumabum, Certolizumab, Certolizumabum, Certolizumab pegol, Golimumab, Golimumabum, Ozoralizumab, Afelimomab, Afelimomabum, Tumor Necrosis Factor Alpha (TNF-) Inhibitors, Tabalumab, Tregalizumab, Anakinra, Basiliximab, Basiliximabum, Daclizumab, Daclizumabum, Tocilizumab, Tocilizumabum, Mepolizumab, Mepolizumabum, Rilonacept, Rilonaceptum, Ustekinumab, Canakinumab, Briakinumab, Fezakinumab, Sirukumab, Sarilumab, Lebrikizumab, Secukinumab, Olokizumab, Gevokizumab, Brodalumab, Ladarixin, Ixekizumab, Dupilumab, Tildrakizumab, Tildrakizumabum, Reslizumab, Reslizumabum, Guselkumab, Guselkumabum, Olamkicept, Fletikumab, Bimekizumab, Mirikizumab, Risankizumab, Abatacept, Ligelizumab, Vedolizumab, Belimumab, Nemolizumab, Tralokinumab, Omalizumab, Benralizumab

Phototherapy or Photochemotherapy:

Programming search of medication name (actual term or preferred term) contains 'photo' then medicals to manually review to confirm whether the medication in question is indeed 'Phototherapy' or 'Photochemotherapy'

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