Statistical Analysis Plan (SAP)

Protocol Title:	A Phase 3b, Open-label Study to Evaluate the Effectiveness and Safety of Lebrikizumab Treatment in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis
Protocol Version No./Date:	M-17923-33 v3.0 / 29-JUL-2024
eCRF Version No./Date:	3.0/20-JAN-2025
SAP Version No./Date:	4.0/18-JUL-2025

1.0 Approvals*

PPD

2.0 Change History

Version/Date	Change Log
0.1/16-Oct-2023	Initial creation by ICON Biotech Solutions.
0.2/25-Oct-2023	Updated eCRF version (v1.0, 19-Oct-2023). Removed the Netherlands from study countries. Clarified CCI endpoint (by domain). Added an "Intercurrent events" section. Included Seed values for supportive endpoints. Clarification on **Section** 12.1 regarding categorical and continuous variables. Clarifications on mTLSS.
1.0/26-Oct-2023	Up-version to 1.0 for signature.
1.1/20-Dec-2023	First draft amendment post-approval including TFL shells (in a separate document) 1. Inclusion of Analysis Visit Windows for Unscheduled Visits (Section 10.1) to clearly detail the process that needs to be followed programmatically. 2. Baseline visit definition allowing the use of Screening value if Baseline value is missing. 3. Removal of "As Observed Analysis" from the list of missing data methodologies as the estimands will not be using that approach. 4. Inclusion of Imputation of missing or partial dates and the logic to derive prior and concomitant medication. 5. Clarification on the number of decimal places to be used for parameters that are programmatically derived (e.g., EASI score). 6. Update in the analyses for Pruritus NRS and Sleep-loss scale scores to use all the available data and not only the ones related with the planned visits. Also, a figure will be added to capture the daily change during the period these questionnaires are reported daily at the beginning of the study.
1.2/20-Feb-2024	1. Clarification of endpoints on CCI and inclusion of endpoint for CCI 2. Clarification on "Treatment Compliance" calculation that it involves only "used syringes" as reported in eCRF. 3. Inclusion of some characteristics in the demographic and baseline variables (i.e. prior exposure to Dupilumab; baseline disease severity; presence of comorbidities; and alcohol and tobacco use) and removal of some patient and investigator-reported outcomes (as they will be part of specific tabulations). 4. Clarification that we will have a separate listing for general medical history, for presence of atopic dermatitis comorbidities, and for substance use for alcohol and tobacco. 5. Inclusion of a separate listing for prohibited concomitant medications. 6. Inclusion of derivations of the score for CCI. 7. Note for subgroup analysis: "*Note that no imputation will be made for those subgroup analyses and selection of subgroups will be done based on the imputed datasets for each respective endpoint*".
2.0/6-MAR-2024	Minor cosmetic changes. **Up-versioning to 2.0 for signature/approval.**

2.1/26-NOV-24	Interim analysis will be performed when approximately 100 patients have completed the study. Clarification that the estimands' framework is not applied to CCI [redacted] and "CCI [redacted]" due to their concept (i.e. no reference level). New Listing for ICE. Clarification on how to use ePRO data windowing for overall ePROs and SCORAD. Clarification on only data from rescreening will be used for analyses. Clarification on the definition of TEAEs. Compliance considers "used and unused syringes" regardless of syringe is returned or not. Clarification on how duration is calculated. Inclusion of "Safety topics of special interest". "SUSAR" wording included for those "related serious TEAEs". Relatedness defined for TEAE. Edits on listing for adverse events. Inclusion of Appendix for Strategy for "Close Events".
2.2/4-DEC-24	Protocol version 3.0 (29-Jul-2024) is approved. Latest eCRF is v2.0 dated 17-Sep-2024. We are implementing all edits required for the IA. However, edits on the nomenclature for study endpoints that are not captured in the most recent approved protocol will be reviewed and amended in the SAP before Database Lock to ensure full alignment with the protocol.
3.0/5-DEC-2024	**Up-versioning to 3.0 for signature/approval.**
3.1/24-FEB-2025	This amendment is performed after the Interim Analysis reported on 14-Jan-2025. Definition of "additional endpoints" not detailed in the protocol. Added clarity on which endpoints will have primary and supportive estimand applied on. Use of min and max option for PROC MI when imputing values. Minimum and maximum values for each questionnaire included on seed tabulation for SAS PROC MI. Added definition for calculating duration (years), and both year and month in days. More categories defined for Demographic and Baseline Characteristics' section. Definition of incidence risk and incidence rate added. Categories defined for eosinophils, bilirubin and liver enzymes. Shift tables and clinically significance for certain laboratory parameters. Tabulation for upper limit of normal (ULN) for liver enzymes and bilirubin. Strategy for "Close events" (appendix).
3.2/24-MAR-2025	Patient-years to be reported per 100 patients. Inclusion of DLQI, CDLQI and BSA of AD involvement in demographic tabulation. Prior and concomitant medication will be summarized in tables and listings for the Safety Analysis Set and not for the Full Analysis Set. Clarification on SAS PROC MI execution on questionnaires.
3.3/31-MAR-2025	Incidence Risk is dropped from the SAP and TFL shells as not required. As confirmed by SCORAD owner, increasing windowing (between patient and investigator's form completion) from ±1 to ±3 days.

	AESIs are categorized based on Adverse Events of Special Interest document provided by Almirall's Safety team. Clarification that for "close events" only TEAEs are checked.
3.4/30-JUN-2025	Update eCRF to v3.0 dated 20-Jan-2025. Adding clarification on **Section 10.12.1.1** as follows: "If the variance between imputed datasets is 0 (i.e. no missing data was imputed), the response rate and 95% CI will be obtained from the first imputed dataset". For TEAE definition (**Section 10.13.2**), examples of lowest level terms and severity are provided to clarify the derivation of TEAE flag. Clarification on Duration formula (**Section 12.1**) to include the start is "Treatment Start Date" and not "Date of First Visit" to match the TEAE definition. Programming was correctly set. Updates on reasons for treatment and study discontinuation (**Section 12.2**) as per the latest CRF. cDLQI threshold modified to <6 and ≥6 in demographic table (**Section 12.3**). Clarification on that TCS is defined by ATC code D07 (**Section 12.4.2.1**). Clarification on that protocol deviation guidance (Section 12.5) is to be finalized before database lock. For Sleep-loss scale, the mean plot has been changed to a stacked bar chart (**Section 12.6.5.3**). As per the TFL shells, including that a listing for "TEAEs leading to study interruption" is generated (**Section 12.7.2**). Updates on abbreviation list.
4.0/18-JUL-2025	**Up-versioning to 4.0 for signature/approval prior to Database Lock.**

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under **Almirall's Protocol M-17923-33** v3.0 dated **29-Jul-2024**.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Endpoints and Estimands
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol v3.0 dated **29-Jul-2024** and electronic case report form (eCRF) v3.0 dated **20-Jan-2025**. Any further changes to the protocol or eCRF may necessitate updates to the SAP.

The final approval of the SAP by Almirall and ICON statisticians and any other Almirall's representative should occur prior to the First Patient In (FPI; "enrolled"). Changes following approval of the first version of the SAP (i.e., v1.0) will be tracked in the SAP Change Log (**Section** 2.0) and the new final version of the amended SAP will be approved prior to final database lock.

6.1 Changes from Protocol

- CCI questionnaire does not include "Side Effects" domain as currently included in the protocol (v3.0; **29-Jul-2024)**
- The investigator will complete two additional questions in the Investigator-Reported Satisfaction Questionnaire.
- Treatment compliance is calculated based on "used/unused syringes" regardless if syringes were returned or not.
- Analysis windows for ePROs will be up to -7 days (prior to study visit) and ±3 day (prior to study visit) for SCORAD (i.e. between patient and investigator's form completion).
- The protocol clearly details the set of endpoints for the study; however, it also states "all additional endpoints will be defined within the SAP". Therefore, we have included "additional endpoints" on **Section** 9.2.

7.0 Study Objectives

7.1 Primary Objective

The primary objective of this study is an effectiveness objective as follows:

- *To evaluate the effectiveness of 24 weeks of lebrikizumab in improving disease severity, signs, and symptoms in adults and adolescents with moderate-to-severe atopic dermatitis (AD).*

Primary objective is composed of **one primary endpoint** and **sixteen secondary endpoints** as described in **Section** 9.2.1.

7.2 Secondary Objective

The secondary objective of this study is a patient- and Investigator-reported outcome measure objective as follows:

- *To evaluate the impact of 24 weeks of lebrikizumab treatment on patient-reported and Investigator-reported outcome measures in adults and adolescents with moderate-to-severe AD.*

Secondary objective is composed of **eighteen endpoints** as described in **Section** 9.2.2.

7.3 Safety Objective

The safety objective of this study is as follows:

- *To evaluate the safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD*

Safety objective is composed of **one safety endpoint** as described in **Section** 9.2.3.

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[redacted]

8.0 Study Design: ADhope

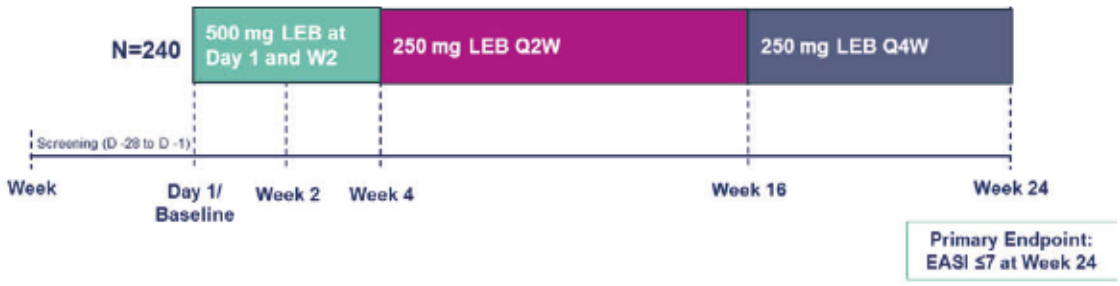
This is a single arm, open-label, Phase 3b study evaluating the effectiveness and safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD. The study will enroll approximately 240 patients.

Patients will be screened for study entry within 4 weeks of study Day 1. For eligible patients, loading doses of lebrikizumab 500 mg subcutaneous (SC) injection will be administered by site personnel at Day 1 and Week 2. Beginning at Week 4, lebrikizumab 250 mg will be administered every other week (Q2W), and patients will have the option of self-administration, following training of the patient and/or caregiver, or the patient may continue to receive injections at the study site. Beginning at Week 16, the dosing frequency will be reduced to every 4 weeks, and patients will receive lebrikizumab 250 mg SC injection every fourth week (Q4W) up to Week 24, the last dose of study medication is given at Week 20.

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

The study design is represented schematically in Figure 1.

Figure 1. Study Design Schematic



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

8.1 Study Rationale

8.1.1 Rationale for Study Design

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

8.1.2 Rationale for Study Population

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

Dupilumab (Dupixent®) is an mAb that was authorised in the EU for the treatment of AD in 2017. Dupilumab binds IL-4Rα, inhibiting IL-4R signalling induced by both IL-4 and IL-13 (Harb & Chatila, 2020). This study will be enrolled such that up to 20% of all patients will have had prior exposure to dupilumab, including those with suboptimal responses. Data on the effectiveness and safety of lebrikizumab in patients previously treated with dupilumab are limited. The results of a subpopulation analysis (N=20) from the ADhere study suggest that patients with prior dupilumab exposure can benefit from lebrikizumab treatment. However, additional data are needed to confirm this finding due to the small number of patients in the subpopulation (Gold *et al.*, 2023). Thus, this study will provide important information to clinicians on the effectiveness and safety of lebrikizumab in both naïve patients and patients previously treated with dupilumab.

8.1.3 Rationale for Study Dose and Regimen

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

8.1.4 Rationale for Study Assessments

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

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

CCI [redacted]

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

Patients will complete treatment CCI [redacted] and the latter will be also applied to Investigators – including two additional questions - to capture their considerations on the patient outcomes.

The timing of the effectiveness and PRO assessments reflects points when meaningful changes from baseline may be expected based on the experience in the pivotal studies, while minimizing the burden on the patients.

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

Table 1. Schedule of Assessments for ADhope Study

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

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

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

[a], Only for patients who withdraw from the study prior to W24, a SFU visit will take place 4 weeks after the last dose of study medication.

[b], Visit window for patient-reported outcomes is -3 days for W2, then -5 days through W16, and -7 days for W24. The window for lebrikizumab self-administration is ±3 days from W4 up to W16 and then ±5 days from Week 16 up to W24.

[c], Height need only be captured at screening.

[d], Serum beta-hCG at Screening for WOCBP, and urine pregnancy testing at all other identified visits. If required per local regulations and/or institutional guidelines, pregnancy testing can occur at other times during the study treatment period. The contraception check is to confirm that contraception, if required, is used consistently and correctly.

[e], Completed eDiary entries for Pruritus NRS are needed for a minimum of 4 out of 7 days in the week preceding Day 1 (Baseline) visit. Then Pruritus NRS to be performed daily up to W2, and weekly from W2 to W16, and every 2 weeks from W16 to W24.

[f], Compliance assessment for study drug, as well as accountability. For patients who discontinue from the study, any unused medication to be returned at the SFU.

[g], Samples for genomic testing will be collected from all consenting patients. A specific consent is required for genomic sampling.

[h], Return of eDiary is applicable only if an electronic device is provided to the patient.

[i], Beginning at Day 1, eligible patients will receive lebrikizumab 250 mg by SC injection Q2W up to W16, except that loading doses of 500 mg will be administered by study site personnel on Day 1 and at Week 2. Patients will have the option of self-administration beginning at W4, following training of the patient and/or caregiver, or the patient may continue to receive injections at the study site. Beginning at W16, the dosing frequency will be reduced to Q4W, and patients will receive lebrikizumab 250 mg SC injection Q4W up to W24 (ie, last Q4W dose administered at W20). For patients who choose to self-administer, sufficient study drug will be dispensed to the patient/caregiver at Weeks 4 and 16 to ensure adequate supplies until the next scheduled study visit.

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

[k], Patient-reported outcomes and quality of life measurements should all be completed before other study assessments. Assessments/procedures are recommended to be conducted in the following order: 1) patient-reported outcomes; 2) Investigator assessments and other effectiveness assessments, 3) safety and laboratory assessments, 4) blood sampling for genomics and CCI and 5) administration of study drug. Note that CCI is not to be completed by the Investigator.

[l], CCI

[m] CCI

[n], mTLSS to be performed only for patients with AD of the hands at Day 1 (Baseline).

8.2 Sample Size Considerations

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

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

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

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

8.3 Randomisation

No randomisation is applicable to this study.

8.4 Blinding

Not applicable as this is an open-label study.

8.5 Eligibility Criteria

Patients will be assessed for inclusion in this study using the criteria identified in the Protocol **Section 8.2 and 8.3**. Once a patient is confirmed to meet all inclusion criteria and none of the exclusion criteria, they will be considered enrolled into the study. This date will be recorded in the eCRF.

9.0 Study Endpoints and Estimands

9.1 Analysis Sets

The following ***Analysis Sets*** will be used in this study.

9.1.1 Full Analysis Set

The Full Analysis Set (***FAS***) is defined as all **enrolled patients**. The analysis of all effectiveness, and patient- and Investigator-reported outcome variables will be performed on the ***FAS***.

9.1.2 Safety Analysis Set

The Safety Analysis Set (***SAF***) is defined as all enrolled patients who receive at least 1 dose of study drug (i.e. lebrikizumab injection). Treatment compliance (both administration and accurate injection technique), all safety and biomarker (available data) variables will be analysed based on the ***SAF***.

9.2 Study Endpoints

Additional endpoints not reported in the protocol but that will be part of the analyses are marked with an asterisk (*) below.

9.2.1 Primary and Secondary Effectiveness Endpoints

Primary Objective*: To evaluate the effectiveness of 24 weeks of lebrikizumab in improving disease severity, signs, and symptoms in adults and adolescents with moderate-to-severe AD.*

Primary Endpoint:

1. Percentage of patients achieving EASI score ≤7 at Week 24.

Secondary Endpoints:

1. Percentage of patients achieving EASI score ≤7 by visit
2. Percentage of patients achieving EASI score ≤5 by visit.
3. Percentage of patients achieving EASI score ≤3 by visit.
4. *Percentage of patients achieving EASI 50 by visit.
5. Percentage of patients achieving EASI 75 by visit.
6. Percentage of patients achieving EASI 90 by visit.
7. *Percentage change in EASI total score from baseline by visit.
8. *Mean EASI score by visit.
9. Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2 points from baseline by visit.
10. *Change in % BSA affected from baseline by visit.
11. *Percentage change in SCORAD from baseline by visit.
12. *Percentage of patients achieving SCORAD 50 by visit.
13. Percentage of patients achieving SCORAD 75 by visit.
14. Percentage of patients achieving SCORAD 90 by visit.
15. Percentage change in mTLSS (hands) from baseline by visit.

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9.2.2 Patient- and Investigator-Reported Outcome Measures Endpoints

Secondary Objective: *To evaluate the impact of 24 weeks of lebrikizumab treatment on patient-reported and Investigator-reported outcome measures in adults and adolescents with moderate-to-severe AD.*

Secondary Endpoints:
Pruritus

1. *Percentage of patients with Pruritus NRS ≥4 at baseline achieving Pruritus NRS score ≤4 by visit.
2. Percentage of patients with Pruritus NRS ≥4 at baseline achieving ≥4-point improvement in Pruritus NRS from baseline by visit.
3. *Percentage change in Pruritus NRS score from baseline by week.

Quality of Life

4. *Change in DLQI/cDLQI from baseline by visit.
5. Percentage of patients achieving DLQI 0-1 by visit.
6. *Percentage of patients with DLQI >5 at baseline achieving DLQI ≤5 by visit.
7. Percentage of patients with DLQI ≥4 at baseline achieving ≥4-point improvement in DLQI from baseline by visit.
8. Percentage of patients achieving cDLQI 0-1 by visit.

9. *Percentage of patients with cDLQI >5 at baseline achieving cDLQI ≤5 by visit.
10. Percentage of patients with cDLQI ≥6 at baseline achieving ≥6-point improvement in cDLQI from baseline by visit.

Sleep Loss Due to Itch

11. Percentage of patients with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least 2-point reduction from baseline by visit.
12. *Change in Sleep-Loss Scale from baseline by week.

Disease Control

13. Percentage of patients with POEM ≥4 at baseline achieving ≥4-point improvement in POEM from baseline by visit.
14. *Percentage change in POEM from baseline by visit.

CCI

[redacted]

9.2.3 Safety Endpoint

Safety Objective: *To evaluate the safety of 24 weeks of lebrikizumab treatment in adults and adolescents with moderate-to-severe AD.*

Safety Endpoints:

1. Percentage of patients with treatment-emergent AEs (TEAEs) including serious adverse events (SAEs), related AEs, and AEs leading to study treatment discontinuation, and adverse event of special interests (AESIs).
2. *Incidence (events per patient-year) of TEAEs (i.e. overall, serious and AESIs) through the study.

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[redacted]

9.3 Study Estimands

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

1. **Treatment of Interest:** Lebrikizumab.
2. **Population**: FAS.
3. **Variable**: Apply to all primary and secondary effectiveness endpoints except for “Patient and Investigator-Reported Satisfaction Questionnaire” and “PGADS”.

4. **How to account for intercurrent events (ICEs):**
   a. Patients who discontinue treatment due to lack of effectiveness during the study will be considered as treatment failures, that is, non-responders, after the ICE. Therefore, a composite strategy (set to baseline) is used for these types of ICE. For patients who discontinue treatment due to any other reasons, a hypothetical strategy will be used to estimate what the treatment effect would have been if the patient had continued with treatment. Therefore, a hypothetical strategy (set to missing; *see* Table 2) is used for these ICE.
   b. Patients who are treated with a prohibited medication for AD during the study will not be considered as treatment failures after the ICE. Therefore, a treatment policy approach (observed) is used for these types of ICE.
5. **Population-level summary:** Response proportions or means.

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

1. **Treatment of Interest:** Lebrikizumab.
2. **Population**: FAS.

- **Variable**: Apply to all primary and secondary endpoints except for CCI [redacted]

3. **How to account for ICEs**:
   a. Patients who discontinue treatment due to lack of effectiveness during the study will be considered as treatment failures, that is, non-responders, after the ICE. Therefore, a composite strategy (set to baseline) is used for these types of ICE. For patients who discontinue treatment due to any other reasons, a hypothetical strategy will be used to estimate what the treatment effect would have been if the patient had continued with treatment. Therefore, a hypothetical strategy (set to missing; *see* Table 2) is used for these ICE.
   b. Patients who are treated with a prohibited systemic medication for AD during the study will be considered as treatment failures after the ICE. Therefore, a composite strategy (set to baseline) is used for these types of ICE.
4. **Population-level summary**: Response proportions or means.

For the estimand of the primary and secondary objectives, missing data including those as a result of ICE will be imputed based on Markov Chain Monte Carlo – multiple imputations (MCMC-MI) as described in **Section** 10.12.

Table 2 summarises the different analyses that will be conducted on the endpoints.

Table 2. Summary on Study Estimands

Estimand	Intercurrent Event			Missing Data Imputation Method
	Treatment Discontinuation		Use of Prohibited Medication for AD[1]	
	Due to Lack of Effectiveness	For Any Other Reason		
Estimand of the primary and secondary objectives (hybrid)	Composite: Set to baseline	Hypothetical: Set to missing	Treatment policy: Observed	MCMC-MI
Supportive estimand (hybrid)	Composite: Set to baseline	Hypothetical: Set to missing	Composite: Set to baseline	MCMC-MI

[1], Only **systemic treatments** will be considered intercurrent event as follows:
1) Immunosuppressive/immunomodulating drugs used for the treatment of atopic dermatitis (e.g., systemic corticosteroids (>30 days), cyclosporine, azathioprine, methotrexate, Janus kinase [JAK] inhibitors, etc.); 2) Any investigational drug used for the treatment of atopic dermatitis; 3) Any other biologic used for the treatment of atopic dermatitis (e.g., dupilumab, tralokinumab).

9.3.1 Intercurrent Events

Two different categories for ICEs will be used in the study:

1. **TREATMENT DISCONTINUATION**:
   a. **Due to lack of effectiveness**. This will be determined as notified in the eCRF by fulfilling the "End of Treatment" page with a reason for discontinuation of "Lack of Effectiveness". In this case, the estimand framework (Table 2) will be implemented subsequent to that time through the end of study.

   b. **For any other reason**. This will be determined as notified in the eCRF by fulfilling the "End of Treatment" page with a reason for discontinuation different from "Lack of Effectiveness". In this case, the estimand framework (Table 2) will be implemented subsequent to that time through the end of study.

2. **USE OF PROHIBITED MEDICATION FOR ATOPIC DERMATITIS**. Only **systemic treatments** will be considered intercurrent event under this category as follows: 1) Immunosuppressive/immunomodulating drugs used for the treatment of atopic dermatitis (e.g., systemic corticosteroids (>30 days), cyclosporine, azathioprine, methotrexate, Janus kinase [JAK] inhibitors, etc.); 2) Any investigational drug used for the treatment of atopic dermatitis; 3) Any other biologic used for the treatment of atopic dermatitis (e.g., dupilumab, tralokinumab).

   If a patient record of a systemic concomitant prohibited medication for AD is found, the estimand framework (Table 2) will be implemented subsequent to that time through end of study.

   Note that ICON Biostatistics & Programming produces a list of programmatically-derived concomitant prohibited medications that will be adjudicated by the Sponsor into "prohibited medication" and/or "systemic medication". Only those medications considered as both "prohibited" and "systemic" will be considered for the estimand framework.

In the primary and supportive estimand, we will use the same approach for those treatment discontinuation's ICEs (Table 2); however, in case of the use of prohibited medication for AD's ICE, a treatment policy (i.e. observed) will be applied for the primary estimand and a composite (i.e. set to baseline) will be applied for the supportive estimand.

A separate tabulation will cumulatively include ICEs by visit for the ***FAS***. A listing will be also provided for the ***FAS*** with the list of ICEs.

10.0 Conventions and Derivations

10.1 Study and Analysis Visit Windows

Table 3 displays study visits, periods, weeks, days, and visit windows.

Table 3. Study Visit Window

Study Visit	Period	Study Week (W)	Analysis Study Day (D)	Study Visit Window (Protocol-defined)	Analysis Visit Window for Unscheduled Visits	
					Lowest Day	Highest Day
1	Screening		D-28 to D-1	-	D-28	D-1
2	Treatment Period	W0	D1 (Baseline)	-	1	1
3		W2	D15	± 3 d	2	22
4		W4	D29	± 3 d	23	71
5		W16	D113	± 5 d	72	141
6		W24	D169	± 7 d	142	176
-	SFU[1]	-	Last dose + 28D	+ 7 d	-	-

D = days; SFU = Safety Follow-up

[1], Only for patients who withdraw from the study prior to W24, a SFU visit will take place 4 weeks after the last dose of study medication.

The schedule of assessments outlined in the protocol (Table 1) specifies the allowable windows for each visit. However, assessments performed outside these protocol-defined windows will not be excluded from any analysis, unless specified otherwise. Therefore, if any assessment is performed outside of window but assigned in eCRF to a target scheduled visit, we will use corresponding data for analysis as assigned to that visit.

On the basis of the visit windows allowed per protocol, applicable programmatic time windowing is introduced to allocate available patient data for unscheduled visits to the pre-defined study time-points. These time windows are summarised in Table 3 and are defined as the mean study day between visits except for Baseline.

This windowing is only to be applied in case the respective endpoint data is missing for a respective scheduled visit. If more than one unscheduled visit with observations is available during one visit window, values will be selected as follows:

- The value – within the visit window specified in Table 3 – closest to the target day in question will be chosen. In case of two values being equidistant to the study day of interest, the observation before the study day in question will be selected.

Importantly, only values recorded at unscheduled visits will be considered for imputation/assignment of missing endpoint data by this windowing. Therefore, values attributed (as part of the eCRF) to a scheduled study visit X will not be allocated to another scheduled study visit Y, even though the date of visit X is outside of the time window for visit X and falls into the time window of visit Y.

As ePRO assessments have a date of completion but they do not have a visit directly assigned on each corresponding form, we will use the start date of the scheduled visit to allocate ePRO data for analysis (e.g.

for Pruritus NRS in Table 15). Similar to CRF data, ePRO assessments performed outside protocol-defined windows will be excluded from analyses except if per the following guidance:

- For all ePROs except SCORAD, the allowed windowing to assign values to **actual visits** is only - 7 days.
- In case of SCORAD this is reduced to only ± 3 days that will be allowed for a discrepancy between the investigator and the patient-reported date of completion. Importantly, patient-information reported via eCRF will be used in case of duplicate information versus the information provided via ePRO. This is due to ensure patient-reported information is completed closer to investigator-reported information.

10.2 Baseline and Change from Baseline

- **Baseline visit** is considered the visit in which the patient initiates the treatment with the investigational medicinal product (IMP) in the ADhope study. If a patient has a missing value in any Baseline assessment which is also captured at Screening, that Screening value will be used as Baseline value. Baseline assessments will be completed for all patients who have completed all screening assessments and met all eligibility criteria. Patients will be considered enrolled once all baseline procedures have been completed and the Investigator has determined that the patient meets the study specific inclusion and exclusion criteria. Any deviation from above logic will be tracked and documented as part of a protocol deviation.
- **Change from Baseline** is defined as:

  [Observed value at post-baseline time point] – [Observed result at study's baseline]
- **Safety follow-up** will only be for patients who withdraw from the study prior to Week 24 i.e. early termination (ET), where it will be performed 4 weeks after the last dose of lebrikizumab.
- **Time point** and **visit** are synonyms within this SAP and TFL shells document.

10.3 End of Study Definition

The "end of study" is defined as the date when all patients enrolled in the study complete Week 24 visit, or discontinue prior to this point.

10.4 Completed Patient Definition

Patients attending the Week 24 visit will be considered **completed patients**.

10.5 Rescreened Patients

Individuals who do not meet the criteria for participation in the study i.e. screen failures may be rescreened once. At the time of rescreening, the individual must sign a new ICF/Informed Assent Form and repeat all Screening procedures. A new ID will be provided. Therefore, only data from rescreening will be used for analyses.

10.6 Replacement of Patients

An enrolled patient who withdraws from the study at any time will not be replaced.

10.7 Study Day Definition

Study Day 1 is defined as the first day of treatment with the IMP in the study, which is also the Baseline visit.

- For dates prior to Study Day 1, the Study Day is calculated as:

$$Study\ Day = Date\ of\ Interest\ or\ Assessment - Date\ of\ Study\ Day\ 1$$

- For dates on or after Study Day 1, the Study Day is calculated as:

$$Study\ Day = (Date\ of\ Interest\ or\ Assessment - Date\ of\ Study\ Day\ 1) + 1$$

10.8 Unscheduled Visit and Test Definition

Unscheduled visit is defined as any additional visit performed at the Investigator's discretion, at any time during the study.

Additional tests outside of the initial schedule of the study will be considered **unscheduled tests** and will not be associated with any study visit.

10.9 Repeated Test Definition

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

For laboratory and non-laboratory parameters, if a patient has more than one measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day (i.e. 12h before target day and 12h after target day), the earlier assessment will be used (i.e. previous day). In case of ties located on the same side of the target day (i.e. more than one value for the same day but different time), the value with the earlier entry date/time will be used. For observations with the same date and time, including missing times and potential baseline values (i.e. prior to first injection), an average of the assessments from these observations will be taken.

If an assessment is determined as "Abnormal" and reason for repeated test is not related with a technical assessment issue, this "Abnormal" value will be used for analysis superseding the above paragraph.

All values will be reported in their respective listings.

10.10 Prior and Concomitant Medication Definition

A medication is considered to be prior if the start date is before the first IMP administration date. A medication is considered to be concomitant if the medication is ongoing at, started together with, or started after the first IMP administration date.

10.11 Drug Accountability, Treatment Exposure and Compliance

Drug accountability, treatment exposure and compliance will be calculated from the items collected on the "Drug Accountability and Administration" eCRF.

Drug accountability will be provided in listings that will include specific items from the "**Drug Accountability and Administration**" section in the eCRF:

- Kit ID
- Date Dispensed
- Syringes Dispensed (it is fixed at 1)*
- Syringe Returned (Yes/No)
- Date Returned
- Syringe Used (Yes/No)
- Any problem with syringe (Yes/No) and reason if yes

* Note that each syringe dispensed will be recorded independently with each associated kit number in the eCRF. Sufficient drug is dispensed to cover injections until the next visit.

Duration of exposure in the study will be calculated as:

$$\boldsymbol{Duration\ of\ Exposure\ (days)} = max\begin{bmatrix} Date\ of\ last\ visit\ (scheduled\ or\ unscheduled) \\ , Date\ of\ last\ dose \end{bmatrix} - Date\ of\ First\ IMP\ administration\ dose\ + 1$$

When the study is still ongoing, before its final lock, there are patients who may have home injections after their last clinical visits, so the maximum date of the last dose or last clinical visit will be used.

Total exposure will be summarised as a continuous variable, and by number and percentage of patients, using the following categories:

- >0, ≥7 days, ≥14 days, ≥30 days, ≥60 days, ≥90 days, >112 days, ≥120 days, ≥150 days. Note that patients may be included in more than 1 category.
- >0 to <7 days, ≥7 to <14 days, ≥14 to <30 days, ≥30 to <60 days, ≥60 to <90 days, ≥90 to <120 days, ≥120 to <150 days, ≥150 days.

Additional exposure ranges may be considered if necessary.

The summaries will also include total exposure in patient-years, calculated as:

$$\textbf{\textit{Total exposure in patient} - \textit{years}} = \frac{Sum\ of\ duration\ of\ exposures\ for\ all\ patients}{365.25}$$

along with the following information:

- Mean, standard deviation (SD), median, 25th and 75th percentiles, minimum and maximum of total dose. Total dose (in mg) is calculated by taking the sum of the number of active injections taken multiplied by respective administered dosage (note it should be 500 mg according to the protocol) for visits Week 0 and Week 2, and the number of active injections taken multiplied by respective administered dosage (note it should be 250 mg according to the protocol) for visits between Week 4 to Week 24, both included.
- Total number of injections administered will be derived from the "**Drug Accountability and Administration**" section in the eCRF.

Treatment compliance will be assessed by counting used or unused prefilled syringes and derived as:

$$\textbf{\textit{Treatment compliance}}\ (\%) = \frac{\#\ injections\ administered\ (used)}{\#\ injections\ expected}\ x\ 100$$

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.

Table 4 include details about the theoretical number of injections administered during the study.

Table 4. Theoretical Number of Injections Administered

Study visit	Week (W)	Injections on Weeks	Number of Expected Injections Since Last Visit[a]	Cumulative Number of Expected Injections Until Each Visit[b]
2	W0	Baseline	2	2
3	W2	2	2	4
4	W4	4	1	5
5	W16	6, 8, 10, 12, 14, 16	6	11
6	W24	20	1	12

a, Each injection is of Lebrikizumab 250 mg. At Baseline and Week 2 two injections are provided to obtain a total dose of 500 mg.
b, Assuming patient follows the dosing regimen as displayed in Figure 1.

10.12 Missing Data

Every effort will be made to prevent patients withdrawing from the study, and for patients who permanently discontinue study drug (and are not lost to follow-up) every effort will be made to continue to collect data

after treatment discontinuation. Missing data in the eCRF will be detected by data management and monitored via edit checks and data analysis.

MCMC-MI will be the imputation method used to handle missing data. Full description of the estimands can be found in **Section 9.3**.

10.12.1 Markov Chain Monte Carlo-Multiple Imputation

This method of imputing missing data will be used to implement the **primary and supportive estimand** of the primary and secondary objectives. Note that this will be used to impute complete score missing data (i.e. item-level missing data will not be imputed and will be handled as described in **Section 12.6**). Baseline visit will be included in the imputation algorithm together with all the post-baseline visits; however, in the eventual case a value is missing at Baseline and it is imputed, it will be set to missing after MCMC-MI.

For patients who discontinue from the study treatment due to lack of effectiveness and/or used prohibited medication for AD (only in the **supportive estimand**), set the patient's baseline value subsequent to this time of discontinuation through Week 24. The MCMC-MI will be used to handle the remaining missing data (i.e. as a result of treatment discontinuation due to any other reason and overall missing data). For each imputation process, 25 datasets with imputations will be calculated. The initial seed values are given in Table 5. The SAS PROC MI with MCMC option (*mcmc chain* = single) will be used to conduct the MCMC-MI. Patients included on each imputation algorithm (i.e. SAS PROC MI) are those who are part of the ***FAS*** except for Face IGA and mTLSS which are further limited to those patients with a non-missing value at baseline. Minimum and maximum options will be included according to each parameter's range (see **Table 5**). Number of iterations will be set to 100000. If by this number of iterations SAS PROC MI is still non-converging, the minimum and maximum options will be removed from the SAS PROC MI and minimum and maximum will be set post-imputation (only if required). Importantly, baseline values will never be imputed. Each complete data set will be analysed with the specified analysis. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

For binary responses related to some endpoints (e.g. EASI and IGA), the binary response variables will be calculated based on the multiple imputed datasets that have been created. Because the MCMC algorithm is based on the multivariate normal model, imputed values for some questionnaires (e.g. IGA and CCI) will not generally be one of the discrete values used in both of their scoring (0, 1, 2, 3, or 4). Therefore, to derive the binary IGA and CCI response variable, standard rounding rules will be applied to the imputed values. Therefore, rounding rules will only be applied to IGA and CCI

For derivation of an EASI 50, EASI 75 and EASI 90 response, no rounding will be performed. The imputed EASI value will be compared directly to the observed Baseline EASI value to determine whether a reduction of at least 50%, 75% or 90% was achieved. Similarly, this logic applies for the SCORAD score.

The approach to handling missing data for Pruritus NRS and Sleep-Loss scale are the same. We use Pruritus NRS as an example. For derivation of the following Pruritus NRS responses, no rounding will be performed. The imputed Pruritus NRS value will be compared directly to the observed mean baseline Pruritus NRS value to determine whether a response was achieved:

- Percentage of patients with Pruritus NRS ≥4 at baseline achieving Pruritus NRS score ≤4 by visit.

Imputation of continuous data will parallel that of binary variables. The imputed values will be used for the secondary effectiveness endpoints such as:

- Percentage change from baseline in EASI total score by visit.
- Percentage change from baseline in Pruritus NRS score from baseline by visit.

Table 5. Seed Values for MCMC-MI

Analysis	Seeds values for primary and supportive estimands	Min-Max
EASI and any related derived endpoints.	768105084	0-72
IGA and any related derived endpoints.	869082151	0-4
CCI		
BSA of atopic dermatitis involvement and any related derived endpoints.	541612315	0-100
SCORAD and any related derived endpoints.	166738773	0-103
mTLSS and any related derived endpoints.	462527179	0-21
Pruritus NRS and any related derived endpoints.	844128291	0-10
DLQI and any related derived endpoints.	663115552	0-30
cDLQI and any related derived endpoints.	596247862	0-30
Sleep-Loss Scale and any related derived endpoints.	505817406	0-4
POEM and any related derived endpoints.	133542365	0-28
CCI		

10.12.1.1 Details of Combining Estimates for Categorial Endpoints with MI

Following the implementation of the MCMC-MI, the 25 data sets with imputations should be set together and sorted by imputation number. This section describes the processes for combining descriptive statistics for the individual imputed data sets into one descriptive statistic for reporting. All calculations are performed in SAS software.

The response rates and their associated standard errors (SEs) are computed for each imputed data set using PROC FREQ. The response rates and SEs from the resulting output are combined across the 25 imputed data sets using PROC MIANALYZE.

Note that the estimate and 95% CI bounds output by PROC MIANALYZE are percentages 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. If the lower or upper limit of the 95% CI is <0 or >100, it will be replaced by 0 or 100, respectively.

If the variance between imputed datasets is 0 (i.e. no missing data was imputed), the response rate and 95% CI will be obtained from the first imputed dataset.

10.12.2 Imputation of Missing or Partial Dates

Imputation of missing or partial dates is described in Table 6 for adverse events, prior or concomitant medication (PM or CM) and medical history. Note that, in listings, original (not-imputed) dates will be presented and any missing date will be represented with a dash symbol (—).

Table 6. Imputation rules for dates

Start Date	Action
Complete missing (Y, M and D)	**AE and PM/CM:** use minimum of ['subject's first visit date' and 'consent date']. **MH:** use minimum of ['subject's first visit date' and ('first dose date' – 1)].
Only M or M & D is/are missing	**AE:** if year('start date of AE')=year(first dose date) then set 'analysis start date' ='first dose date' else use 1st January. **PM/CM and MH:** use 1st January.
D is missing	**AE:** if year(start date of AE) = year(first dose date) and month(start date of AE)=month(first dose date) then set 'analysis start date'='first dose date' else use 1 (first day of the month) **PM/CM and MH:** use 1 (first day of the month)
Stop Date	**Action**
Complete missing (Y, M and D)	**AE and PM/CM:** use subject's last visit date. **MH**[1]**:** use subject's last visit date.
Only M or M & D is/are missing	**AE, PM/CM and MH:** use 31st December.
D is missing	**AE and PM/CM:** use last day of the month. **MH:** use last day of the month. However, record should not be expanded past patient's last visit.

Abbreviations: AE = adverse event; CM = concomitant medication; D = day; M = month; MH = medical history; Y = year.

[1], if "Ongoing" is not selected.

Note: If the imputed 'analysis start date' > [non-imputed 'analysis end date' or available 'partial end date'], set 'analysis start date' = 'analysis end date'.

Note: If the imputed 'analysis end date' < [non-imputed 'analysis start date' or available 'partial start date'], set 'analysis end date' = 'analysis start date'.

Note: For MH, as screen fail patients do not have 'subject's first visit date' nor 'first dose date', completely missing start and/or end dates will not be imputed.

Table 7 will be used to derive prior and concomitant medications based on the availability of start and/or end dates after the imputation of missing or partial date is conducted for PM or CM.

Table 7. Derivation of prior and concomitant medications

Start Date	Stop Date	Action
Known	Known	If stop date < study med start date, assign as PM If stop date ≥ study med start date and start date ≤ EoT period[1], assign as CM
	Partial	Impute stop date as per Table 6, then apply the above row's assumptions.
	Missing	If stop date is missing it could never be considered a PM. If start date ≤ EoT period[1], assign as CM
Partial	Known	Impute start date as per Table 6, then: If stop date < study med start date, assign as PM If stop date ≥ study med start date and start date ≤ EoT period[1], assign as CM
	Partial	Impute start date and stop date as per Table 6, then apply the above row's assumptions.
	Missing	Impute start date as per Table 6, then: If stop date is missing it could never be assumed as PM If start date ≥ Study med start date and ≤ EoT period[1], assign as CM
Missing	Known	If stop date < study med start date, assign as PM If stop date ≥ study med start date, assign as CM
	Partial	Impute stop date as per Table 6, then apply the above row's assumptions.
	Missing	Assign as CM

Abbreviations: CM = concomitant medication; EoT = end of treatment; med = medication; PM = prior medication; Post-TM = post-treatment medication.
[1], W20 is last treatment administration.

10.13 Definition of Types of Adverse Event

10.13.1 Adverse Event Definition

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

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

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

Appendix 1 describes how to programmatically merge consecutive AEs when these are considered as close events (i.e. end date and start date of the record are the same with a maximum of 1 day gap between events). Note that only TEAEs will be checked.

10.13.2 Treatment-Emergent Adverse Event Definition

TEAEs are undesirable events that first occurred or worsened in severity after the date of first IMP injection in the study, and on or prior to the date of the last visit within the treatment period.

AEs will be collected only once with its maximum severity, except when the AE started before first IMP administration, persisted after it and worsened in severity any time after first IMP. In this latter case, the AE

will be collected with each respective severity. AE term recorded must be exactly the same in the different timepoints where AE is reported in the eCRF.

During the trial (and for each patient), each AE lowest level term (LLT; variable *AELLT* in ADAE dataset) will be compared to any Baseline LLT (*BASELLT*; i.e., any LLT that started prior to IMP administration); if there is an LLT-match, the AE severity (*AESEV*) will be compared to Baseline severity (BASESEV) and the flag for treatment emergent AE (*TRTEMFL*) will be modified as follows:

- If AESEV ≤ BASESEV, then TRTEMFL = N.
- If AESEV > BASESEV, then TRTEMFL = Y.

Examples can be found on Table 8.

Table 8. TEAE Flag Derivation Based on LLT and Baseline Severity

LLT (*AELLT*)	AE Start Day (*AESTDY*)	AE End Day (*AEENDY*)	AE Severity (*AESEV*)	Baseline Severity (*BASESEV*)	Baseline LLT (*BASELLT*)	TE Flag (*TRTEMFL*)
LLT1	-10	-5	Mild	Mild	LLT1	N
LLT1	10	20	Mild	Mild	LLT1	N
LLT2	-10	-5	Mild	Mild	LLT2	N
LLT2	10	20	Moderate	Mild	LLT2	**Y**
LLT3	-10	5	Mild	Mild	LLT3	N
LLT3	20	30	Moderate	Mild	LLT3	**Y**
LLT4	-80	16	Moderate	Moderate	LLT4	N
LLT4	250	260	Moderate	Moderate	LLT4	N
LLT5	-10	12	Mild	Mild	LLT5	N
LLT5	60	70	Moderate	Mild	LLT5	**Y**
LLT5	100	110	Mild	Mild	LLT5	N
LLT6	-5	17	Mild	Mild	LLT6	N
LLT6	80	91	Moderate	Mild	LLT6	**Y**
LLT6	102	106	Moderate	Mild	LLT6	**Y**

LLT = Lowest Level Term; TE = Treatment Emergent.
Note: Word in parenthesis is the ADaM variable in ADAE dataset.

10.13.3 Adverse Events of Special Interest

The following TEAEs are being designated as AESIs:

- Conjunctivitis.

- Herpes simplex or zoster infection.
- Parasitic infections.

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

10.13.4 Adverse Events of Safety Topics of Special Interest

The categories and sub-categories describing the AE of safety topics of special interest are detailed in the most updated version of the Safety Topics of Special Interest which is provided as a separate document. The complete list of the preferred terms (PTs) will be confirmed prior to database lock and included in the final outputs. The categories for AESIs are collected in the eCRF, however, to prevent erroneous manual categorizations, AESIs will be categorized in the analysis based on the Adverse Events of Special Interest document provided by Almirall's Safety team.

10.13.5 Serious Adverse Event

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

- Results in **death.**
- Is **life-threatening** (i.e. an event which, in the view of the Investigator, places the patient at immediate risk of death from the event as it occurred). It does not mean that the event might hypothetically have caused death if it was more severe or lasted longer.
- Requires **in-patient hospitalisation** or **prolongs** existing hospitalisation. Hospitalisation is defined as an overnight stay at the hospital or emergency room. Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician.
- Results in persistent or significant **disability** or **incapacity**.
- Is a **congenital anomaly** or **birth defect**.
- Is any **other medically important event** that may jeopardise the patient or may require intervention to prevent one of the other above outcomes.

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

11.0 Interim Analyses

An interim analysis (IA) would allow a preliminary evaluation of assessments not previously performed in study patients treated with lebrikizumab, including the CCI mTLSS, CCI [redacted]. Additionally, it would inform on clinical outcomes in patients previously treated with dupilumab.

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

As the study is open-label, no unblinding needs to occur and as such the interim analyses will be performed when necessary by the ICON team. A Data Review Meeting may be done just before the database lock to document decisions taken on population assignment.

12.0 Statistical Methods

12.1 General Considerations

All analyses will use SAS® version 9.4 or higher. Table and listing outputs will be presented using ICON standard layouts. Unless specified otherwise:

Categorical variables will be summarised using counts and percentages (n [%]). Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Number of responders and 95% CIs – calculated using asymptotic method without continuity correction (i.e., normal approximation to the binomial distribution) – will be provided for **observed data**. For **primary and supportive estimands**, number of responders will be also provided, however, 95% CIs will be calculated following Rubin (1987) based on estimates and standard errors from each imputation process.

In case of **observed data**, percentage of responders will be determined from the number of patients with non-missing values. The same will apply to primary and supportive estimands in the eventual case a value is missing at Baseline.

Continuous variables will be summarised as follows:

- For **observed data**: using the number of observations (n, non-missing cases), mean, SD, median, minimum, 25th and 75th percentiles, and maximum.
- For **estimands**: using the number of observations (n, non-missing cases), mean, standard error of the mean (SEM), and 95% CI.

The minimum and maximum values will be displayed to the same level of precision as the raw data; the mean, median, 25th and 75th percentiles, and 95% CI to a further decimal place; the SD and SEM to two additional decimal places to a maximum of four. When the raw value of a parameter (e.g. EASI score) is programmatically derived, it will be considered with only one decimal place, including its mean, 95% CI, median, minimum, 25th and 75th percentiles and maximum, whereas SD and SEM will have two decimal places.

No *P*-values will be derived as only descriptive analyses will be included in the study.

$$\textbf{Duration (years)} = (\text{Date of event or Date of Last Visit in ADhope study [if event not occurred]} - \text{Treatment Start Date} + 1) / 365.25$$

Per the calculations on the study:

- A year is considered as 365.25 days.
- A month is defined as 30.5 days.

As Pruritus NRS and Sleep-Loss Scale is a daily, weekly and Q2W/Q4W PRO, nmiss will specifically assess if the (prorated) weekly value for the corresponding visit is present respectively.

If a non-zero value is rounded to zero, it will be presented as “<0.1” (“<0.01”, etc. depending on data precision respectively).

Importantly, as part of good practices for statistical programming, any already derived value at eCRF level for investigator’s awareness (e.g. total EASI score) will be recalculated from its raw data prior to creating outputs following the calculations and instructions provided in this SAP.

12.2 Patient Disposition

The number and percentage of patients screened and included in each analysis set will be presented for the ***All Screened Patients*** set. Additionally, the number and percentage of patients enrolled at each centre and overall will be presented by country for the ***FAS***. Furthermore, the number and percentage of patients who completed the treatment/study, are ongoing on treatment/study, withdrew from the treatment/study prematurely and a breakdown of the corresponding reasons for withdrawal will be presented for the ***FAS***. A separate tabulation will summarise the number of patients in the study by visit for the ***FAS***.

The following reasons, as specified in the eCRF, will be included in the disposition tables (for ***FAS***) and/or listings (for ***FAS***):

- **Reasons for non-enrolment:**
  - Failed Inclusion / Met Exclusion Criteria.
  - Withdrawal of Consent.
  - Lost to Follow-Up.
  - Other.
- **Reasons for treatment discontinuation (end of treatment)**:
  - Adverse Event.
  - Intercurrent Illness.
  - Laboratory Abnormality.
  - Lack of Effectiveness.
  - Pregnancy.
  - Withdrawal by Subject.
  - Withdrawal by Parent/Guardian.
  - Other.
- **Reasons for study discontinuation (end of study)**:
  - Adverse Event.
  - Lost to Follow Up.
  - Pregnancy.
  - Physician Decision.
  - Protocol Deviation.
  - Study Terminated by Sponsor.
  - Withdrawal by Subject.
  - Withdrawal by Parent/Guardian.
  - Other.

12.3 Demographic and Baseline Characteristics

The study population will be described using demographic and baseline characteristics recorded before the first study treatment administration in the study (during the screening period). Analyses of demographic and baseline characteristics will be based on the ***FAS***. Listings will be provided for ***FAS***.

Appropriate descriptive statistics will be used to summarise demographic and baseline characteristics as highlighted in **Section** 12.1. No statistical tests will be performed.

Demographic and baseline variables will include:

- **Age** at informed consent (years).
- **Age group:** Adolescents (12 to <18 years); Adults (≥18 years).
- **Sex at birth**: Female; Male.
- **Country**: Germany; the Netherlands; the United Kingdom.
- **Prior exposure to Dupilumab**: Yes/No; by Country.
- **Baseline Disease Severity**: Baseline EASI score ≥ 12 to <16; Baseline EASI score ≥ 16.
- **EASI:** continuous
- **IGA:** continuous and categorical (3 and 4)
- CCI [redacted]
- **Pruritus NRS:** continuous and categorical (<4 and ≥4)
- **Sleep-loss scale**: continuous and categorical (<2 and ≥2)
- **Fitzpatrick scale:** categorical (I; II, III; IV; V; and VI)
- **mTLSS:** continuous
- CCI [redacted]
- **DLQI:** continuous and categorical (<4 and ≥4)
- **cDLQI:** continuous and categorical (<6 and ≥6)
- **BSA of AD involvement:** continuous
- **Ethnicity**: Hispanic or Latino; Not Hispanic or Latino; Not Reported; Unknown.
- **Race (multiple choices are allowed)**: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Multiple; Other; Not Reported; Unknown.
- **Weight** (kg).
- **Weight group**: <60 kg; ≥60 to <100 kg; ≥100 kg.
- **Height** (cm).
- **Body Mass Index** (BMI, kg/m^2).
- **BMI group**: Underweight (<18.5 kg/m^2); Normal (≥18.5 to <25 kg/m^2); Overweight (≥25 to <30 kg/m^2; Obese (≥30 to <40 kg/m^2); Extreme Obese (≥40 kg/m^2); Not Calculated. Only reported for adults ≥18 years.
- **Duration Since AD Onset** (years): duration from diagnosis to Baseline visit.
- **Presence of comorbidities:** Asthma; Alopecia Areata; Food Allergy; Allergic Rhinitis; Eosinophillic Esophagitis.
- **Past comorbidities:** Conjunctivitis; Herpes Zoster; Chicken-pox; Eczema Herpeticum; Herpes Labialis; Genital Herpes; Chronic Hand Eczema; and, Prurigo Nodularis.
- **Alcohol use (items: wine, beer and/or spirits):** never, former or current.
    - "Never" stands for patients reporting "Never" consumed any item from alcohol category.

- "Former" stands for patients reporting "Former" at least on one item of alcohol category and no item is reported as "Current" on alcohol category.
- "Current" stands for patients reporting "Current" at least on one item on alcohol category.
- If all items from the category are missing, the full category will be shown as missing.

- **Tobacco use (items: cigarettes, cigars and/or pipes):** never, former or current. Same logic as for Alcohol use.

12.3.1 Medical History

Information regarding medical history will be presented in tables for ***FAS***. The number and percentage of patients with each medical history term will be summarised by system organ class (SOC) and preferred term (PT). Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 or higher to assign a SOC and PT to each event. Separate listings for general medical history, presence of atopic dermatitis comorbidities (tabulated in demographics), and substance use for alcohol and tobacco (tabulated in demographics) will be included for ***FAS***.

12.4 Treatments

12.4.1 Extent of Treatment Exposure

The duration of the treatment (first dose to last dose) is 20 weeks. The total duration of each patient's participation in the study is estimated at up to 24 weeks. Exposure to lebrikizumab is as detailed in **Table 4**. The duration of exposure and treatment compliance detailed in **Section 10.11** will be summarised and provided in the listings along with drug accountability in listings for ***SAF***.

12.4.2 Prior and Concomitant Medications

Medications received prior or concomitantly with study drug (preferred base name), categorised by Anatomical Therapeutic Chemical (ATC) medication subgroup (ATC level 4) or subgroup (ATC level 3, 2 or 1, if level 4 is not available) according to World Health Organization (WHO) Drug Version March 2023 or later will be summarised for the ***SAF*** in tables and listings. The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each medication group and subgroup.

12.4.2.1 Allowed Concomitant Medication

Permitted concomitant medications during the study include:

- Non-medicated moisturizers are to be used during the study. Patients may continue to use her/his current over-the-counter moisturizer regimen, if approved by the Investigator.
- Lebrikizumab monotherapy is recommended, but the concomitant use of low and mid-potency topical corticosteroids (TCS) is permitted, per the Investigator's discretion, for patients on a stable regimen at baseline. The baseline TCS regimen and any changes during the study will be captured in the eCRF.
- Intermittent use of other topical medications (i.e. topical calcineurin inhibitors and topical phosphodiesterase-4 inhibitors) is permitted for the treatment of worsening AD symptoms during the study.
- Acute infections can be treated with systemic antibiotics.

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

Note that TCS is defined with ATC code D07:

- High Potency TCS, with the following ATC codes: D07AC, D07AD, D07BC, D07BD, D07CC, D07CD, D07XC or D07XD.
- Low or moderate potency TCS, with ATC code D07, excluding D07AC, D07AD, D07BC, D07BD, D07CC, D07CD, D07XC or D07XD.

12.4.2.2 Prohibited Concomitant Medication

Both prior and concomitant use of tralokinumab and oral JAK inhibitors is prohibited. Prior use of dupilumab is allowed, following a 8-week washout prior to Day 1/Baseline, but concomitant use of dupilumab is prohibited. The concomitant use of systemic corticosteroids for the treatment of AD is prohibited, except as specified in **Section** 12.4.2.1. Chronic treatment with systemic antibiotics for infections is not permitted.

Other drugs that are prohibited during the study are listed in **Table 9**, but prior use is permissible after expiration of the washout period.

A separate listing will include prohibited concomitant medications for the ***FAS***.

Table 9. Prohibited Concomitant Medications and Washout Period for Prior Use

Prohibited Medications	Washout Period Prior to Baseline
High-potency TCS except for short-term use as specified in **Section** 12.4.2.1 Topical calcineurin inhibitors and phosphodiesterase-4 inhibitors, such as crisaborole, except for intermittent use as specified in **Section** 12.4.2.1; cannabinoid treatment for AD	2 weeks
• Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids (>30 days), cyclosporine, mycophenolate-mofetil, interferon-γ, azathioprine, methotrexate, etc.) • Phototherapy and photochemotherapy for AD • Regular use (more than 2 visits per week) of a tanning booth/parlour	4 weeks
An investigational drug	8 weeks or 5 half-lives (if known), whichever is longer
Dupilumab	8 weeks
Live (attenuated) vaccine	12 weeks
Other biologics	16 weeks or 5 half-lives (if known), whichever is longer
B cell-depleting biologics, including but not limited to rituximab	6 months

12.5 Protocol Deviations

Any protocol deviations during the conduct of the study will be recorded by Clinical Research Associate/Monitors as detected or derived from data collected in the clinical database. Per ICON Biotech Solutions processes, protocol deviations data will be entered into our system of record (Predictivv Study Operations [PSO]). The study team and the sponsor will conduct ongoing reviews of the deviation data from PSO and the resulting set of evaluable patients throughout the study, adjusting the deviation criteria as seems appropriate. Relevant deviations will be promptly reported to the Sponsor after detection. Protocol deviations are categorised as non-important or important as per the protocol deviation guidance document

and finalised during a Data Review Meeting before database lock. Important protocol deviations will be included in the corresponding listing of the clinical study report.

Based on the protocol deviations data entered into PSO, the protocol deviations thought to potentially impact the statistical analyses or patient safety (i.e. important protocol deviations) will be tabulated and listed for ***FAS*** using number and percentage of patients. Protocol deviations are defined in the current version of the protocol deviation guidance document. The last approved version of the protocol deviation guidance will be finalised before the database lock.

12.5.1 Impact of COVID-19 or Any Other Pandemic Outbreak

During the initial writing of this SAP (i.e., late 2023) Coronavirus Disease 2019 (COVID-19) was a concerning topic but with a reduced predicted impact on study progression as both prevalence and incidence rates are currently not as high/alarming as during 2020-2022 period. However, any impact of COVID-19 or any other pandemic outbreak on analyses will be addressed in the study. In general, any missing assessments/visit window will be documented as protocol deviations.

COVID-19 status and/or other generalised situations that may impact the course of the study will be monitored during the development of the study. Therefore, if the circumstances worsen during the study (i.e. increased incidence affecting study's execution), the SAP will be amended to incorporate further sensitivity and/or subgroup analysis, as appropriate.

12.6 Effectiveness Analyses

All effectiveness, patient- and Investigator-reported outcomes endpoints/analyses will be presented on ***FAS*** in both tables and listings. All these tabulations – except for CCI [redacted] - will include three columns to report results: i) as observed; ii) following primary estimand; and, iii) following supportive estimand. Exploratory endpoints/analyses will be presented on ***SAF*** in both tables and listing.

A summary of the assessments that will be used during the study for the different endpoints is included in Table 10. All the primary and secondary effectiveness endpoints will be assessed starting at Day 1/Baseline and finishing at Week 24/ET.

Table 10. Summary of Effectiveness, and Patient and Investigator-Reported Outcome Assessments

Assessment	Source	Description	Frequency	Variable
EASI	eCRF	**Items for severity**: 4 (erythema; induration/papulation; excoriation; lichenification). **Score for each item for severity**: 0 (none); 1 (mild); 1.5 (mild to moderate); 2 (moderate); 2.5 (moderate to severe); 3 (severe). **Items for area**: 4 (Head/neck [x0.1]; Trunk [x0.3]; Upper extremities [x0.2]; Lower extremities [x0.4]). **Score for items for body area**: % body area converted to 0 (0%) to 6 (90-100%). **Total score range**: 0 to 72 (indicating most severe). **Score per body area =** Total score for all severity item x Score for 1 area item x constant i.e. 0.1 **EASI score** = sum of all scores per body area (up to 72)	Week 24	Percentage of patients with EASI score ≤7
			By visit	Percentage of patients with EASI score ≤7, ≤5, and ≤3
				Percentage of patients achieving EASI 50, EASI 75 and EASI 90
				Percentage change from baseline in EASI total score
				Mean EASI score
IGA	eCRF	**Range**: 5-point scale. **Score**: 0 (clear) to 4 (severe).	By visit	Percentage of patients with IGA score of 0 or 1 and a reduction ≥2 points
CCI				

Assessment	Source	Description	Frequency	Variable
BSA of AD Involvement	eCRF	**Item**: Percentage of total body surface; using patient palm=1% BSA rule. **Areas**: Below are estimates when entire areas (anterior and posterior) are covered: Head and Neck = 10% (10 palms); Upper Extremities = 20% (20 palms); Trunk (axillae and groin) = 30% (30 palms); Lower extremities (buttocks) = 40% (40 palms) **Total BSA** = 100% (100 palms)	By visit	Change in % BSA affected from baseline
SCORAD	eCRF (Investigator) and electronic diary (eDiary/eCRF[a]) [Patient]	**AD surface involvement or extent (A)** – Investigator Proportion of involved surface area segment by segment by applying the rule of 9 and reported as the sum of all areas. Score range: 0 to 100. **Intensity (B)** - Investigator Items: 6 (erythema; oedema; oozing/crusting; excoriation; lichenification; dryness). Score range: 0 (none); 1 (mild); 2 (moderate); 3 (severe). Maximum total score: 18. **Subjective symptoms (itch, sleeplessness) [C]** – Patient Uses visual analog scale (VAS) for each symptom. Score range: 0 (no itch [or sleeplessness]) to 10 (worst imaginable itch [or sleeplessness]). Maximum possible score: 20. **SCORAD Index formula** = A/5 + 7B/2 + C. **Maximum SCORAD Index**: 103.	By visit	Percentage change in SCORAD from baseline Percentage of patients achieving SCORAD 50, SCORAD 75 and SCORAD 90

Assessment	Source	Description	Frequency	Variable
mTLSS	eCRF	**Items**: 7 features of AD of the hand (erythema; scaling; lichenification/hyperkeratosis; vesiculation; oedema; fissures; pruritus/pain). **Score per item**: 0 (none) to 3 (severe). **Total score range**: 0 to 21. It is performed only for the most affected side of the most affected hand.	By visit	Percentage change from baseline in mTLSS (hands)
Pruritus NRS	eDiary	**Range**: 11-point scale. **Score**: 0 (No itch) to 10 (Worst itch imaginable).	By visit[b]	Percentage of patients with Pruritus NRS ≥4 at baseline achieving Pruritus NRS score ≤4
				Percentage of patients with Pruritus NRS ≥4 at baseline achieving ≥4-point improvement in Pruritus NRS from baseline
				Percentage change in Pruritus NRS score from baseline
DLQI	eDiary	**Items:** 10 (symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex and treatment). **Score per item**: 0 (not at all); 1 (a little); 2 (a lot); 3 (very much). **Total score range:** 0 to 30 (indicating poorest quality of life (QoL).	By visit	Change in DLQI from baseline
				Percentage of patients achieving DLQI 0-1
				Percentage of patients with DLQI >5 at baseline achieving DLQI ≤5

Assessment	Source	Description	Frequency	Variable
				Percentage of patients with DLQI ≥4 at baseline achieving ≥4-point improvement in DLQI from baseline
cDLQI	eDiary	**Items:** 10 (symptoms; embarrassment; friendships; clothes/shoes; leisure/hobbies; swimming/sports; school/holidays; teasing/bullying; sleep; treatment). **Score per item**: 0 (not at all); 1 (only a little); 2 (quite a lot); 3 (very much). **Total score range:** 0 to 30 (indicating poorest QoL)	By visit	Change in cDLQI from baseline
				Percentage of patients achieving cDLQI 0-1
				Percentage of patients with cDLQI >5 at baseline achieving cDLQI ≤5
				Percentage of patients with cDLQI ≥6 at baseline achieving ≥6-point improvement in cDLQI from baseline
Sleep-Loss Scale	eDiary	**Range**: 5-point Likert scale. **Score**: 0 (not at all) to 4 (unable to sleep at all).	By visit[c]	Percentage of patients with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least 2-point reduction
				Change in Sleep-Loss Scale from baseline
POEM	eDiary	**Items:** 7 (skin dryness; itching; flaking; cracking; sleep loss; bleeding; weeping). **Score per item**: 0 (No days); 1 (1-2 days); 2 (3-4 days); 3 (5-6 days); 4 (every day).	By visit	Percentage of patients with POEM ≥4 at baseline achieving ≥4-point improvement in POEM from baseline

Assessment	Source	Description	Frequency	Variable
		Total score range: 0 (clear or almost clear) to 28 (very severe eczema).		Percentage change in POEM from baseline

CCI

[redacted]

[a], Initially, Patient-part was collected from eDiary; however, from 25-Oct-2024, eCRF was the collection method.

[b], Completed eDiary entries for Pruritus NRS are needed for a minimum of 4 out of 7 days in the week preceding Day 1/Baseline visit. Then Pruritus NRS to be performed daily up to Week 2, and weekly from Week 2 to Week 16, and every 2 weeks from Week 16 to Week 24.

[c], Completed eDiary entries for Sleep-Loss Scale are needed for a minimum of 4 out of 7 days in the week preceding Day 1/Baseline visit. Then the Sleep-Loss Scale is to be performed daily up to Week 2, weekly from Week 2 to Week 16, and every 4 weeks from Week 16 to Week 24.

12.6.1 Hypothesis Testing Strategy and Multiplicity

No inferential statistical analysis will be performed. Effectiveness endpoints will be summarised by means of descriptive statistics for this open-label study.

No multiplicity adjustment will be applicable due to the descriptive nature of the analyses.

12.6.2 Imputation Methods

A MCMC-MI method will be used in all primary and secondary effectiveness analysis with the intention of describing completed data. Exception to this are ”Patient and Investigator-Reported Satisfaction Questionnaire” and “PGADS” which will be only subject to “Observed” analysis.

12.6.3 Primary Effectiveness Analysis and Endpoint

The primary effectiveness endpoint which is the percentage of patients achieving EASI score ≤7 at Week 24 will be included in tables and listings for ***FAS***.

12.6.3.1 Eczema Area and Severity Index Score

The EASI is used to assess the severity and extent of AD. It is a composite index with scores ranging from **0 to 72**, with higher values indicating more severe and or extensive disease (Hanifin *et al.*, 2001). The severity of erythema, induration/papulation, excoriation, and lichenification will be assessed by the Investigator or trained designee on a scale of 0 (absent) to 3 (severe) for each of the **four body areas**: head/neck, trunk (including the genital area), upper extremities, and lower extremities (including the buttocks), with half points allowed starting from 1 as follows:

0: None	**1**: Mild	**1.5**: Mild to Moderate	**2**: Moderate	**2.5**: Moderate to Severe	**3**: Severe

In addition, the extent of AD involvement in each of the 4 body areas will be assessed as a percentage by body area of head/neck, trunk, upper extremities, and lower extremities, and converted to a score of 0 to 6 as follows:

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

A separate **‘intermediate’ EASI score** is calculated in the eCRF for each of the four body areas. This value is then multiplied by a factor depending on the body area as follows: head/neck (x0.1); trunk (x0.3); upper extremities (x0.2); lower extremities (x0.4), to derive a **score per body area**. The sum of all four score per body area produces the (final) **EASI score** which is included in the eCRF. Details on EASI calculation are included in **Table 11**.

(!) Note that, if any area is left unanswered the total score will not be calculated.

Table 11. EASI Score Calculation For Patients ≥8 Years

Body Area	Erythema (0-3)	Oedema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region Score (0-6)	Multiplier	Score Per Body Area
Head/neck	(+	+	+	)	x	x 0.1	
Trunk	(+	+	+	)	x	x 0.3	
Upper extremities	(+	+	+	)	x	x 0.2	
Lower extremities	(+	+	+	)	x	x 0.4	
The final EASI score is the sum of the 4 area scores							(0-72)

12.6.4 Secondary Effectiveness Analyses and Endpoints

All secondary effectiveness analyses are summarised in tables and listed for the ***FAS.***

12.6.4.1 Eczema Area and Severity Index Score

Details on EASI score are explained in Section 12.6.3.1.

EASI x (where 'x' is a threshold such as 50, 75 or 90) is defined as a ≥x% reduction in EASI score from baseline. Using the EASI calculated for each visit and the baseline value, the change from baseline for EASI will be derived and whether each patient at each visit meets EASI 50, EASI 75, or EASI 90.

Appropriate subgroup analysis (**Section** 12.6.7) will be performed for ***FAS***.

The following information will be summarised in the tables and provided in the listings for ***FAS***:

- Percentage of patients achieving EASI score ≤7, EASI ≤5, and EASI ≤3 by visit.
- Percentage of patients achieving EASI 50, EASI 75, and EASI 90 by visit.
- Percentage change in EASI total score from baseline by visit.
- Mean EASI score by visit.

12.6.4.2 Investigator Global Assessment

The IGA is an instrument used to globally rate the severity of the patient's AD. It is based on a 5-point scale ranging from 0 (clear) to 4 (severe), and a score is selected using descriptors that best describe the overall appearance of the lesions at a given time point (Table 12).

Table 12. Investigator Global Assessment Rating

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

Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2 points from baseline by visit will be summarised and provided in the listings for ***FAS***.

12.6.4.3 Body Surface Area of AD Involvement

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the patient palm=1% BSA rule.

Below are estimates when entire areas (anterior and posterior) are covered:

- Head and Neck = 10% (10 palms).
- Upper Extremities = 20% (20 palms).
- Trunk (axillae and groin) = 30% (30 palms).
- Lower Extremities (buttocks) = 40% (40 palms).

TOTAL BSA = 100% (100 palms).

(!) Note that, if any area is left unanswered the total score will not be calculated.

The change in % BSA affected from baseline by visit will be summarised and included in listings for ***FAS.***

CCI

12.6.4.5 Scoring Atopic Dermatitis

The SCORAD is used to assess the extent and intensity of AD (ETFAD, 1993). There are 3 components to the assessment:

- **Extent**: The AD surface involvement: the proportion of involved surface area segment by segment by applying the rule of 9s (i.e. 50% of the right leg = 4.5) and reported as the sum of all areas, with a score ranging from 0 to 100.
- **Intensity**: The intensity part of the SCORAD consists of 6 items: erythema, oedema, oozing/crusting, excoriation, lichenification, and dryness. Each item is graded as follows: Absence (0), Mild (1), Moderate (2), or Severe (3), for a maximum of 18 total points.

- **Subjective symptoms**: Subjective assessment of itch and of sleeplessness: recorded for each symptom using VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), for a maximum possible score of 20.

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

Assessments will be reported by the clinician and the patient (VAS only).

SCORAD x (where 'x' is a threshold such as 50, 75 or 90) is defined as a ≥x% reduction in SCORAD score from baseline. Using the SCORAD calculated for each visit and the baseline value, the change from baseline for SCORAD will be derived and whether each patient at each visit meets SCORAD 50, SCORAD 75, or SCORAD 90.

The following information will be summarised and provided in the listings for ***FAS***:

- Percentage change in SCORAD from baseline by visit.
- Percentage of patients achieving SCORAD 50, SCORAD 75, and SCORAD 90 by visit.

12.6.4.6 Modified Total Lesion Symptom Score

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

(!) Note that, if any feature is left unanswered the total score will not be calculated.

Percentage change from baseline in mTLSS (hands) by visit will be summarised and provided in the listings for ***FAS***. This will be done only for those patients with a baseline value for mTLSS.

12.6.5 Patient- and Investigator-Reported Outcomes' Endpoints

12.6.5.1 Pruritus Numerical Rating Scale

The Pruritus NRS is an **11-point scale** used by patients to rate their worst itch severity over the past 24 hours, with 0 indicating "No itch" and 10 indicating "Worst itch imaginable" (Phan *et al.*, 2012). The baseline Pruritus NRS will be determined based on the average of daily Pruritus NRS scores during the 7 days immediately before the Day 1/Baseline visit. A minimum of 4 daily scores out of the 7 days immediately before Day 1/Baseline visit is required for this calculation. Assessments will then be recorded daily from Day 1/Baseline up to Week 2, weekly from Week 2 to Week 16, and every 2 weeks from Week 16 to Week 24.

As the Pruritus NRS consists of a daily, prorated weekly and Q2W PRO, all these values will be provided in listings for ***FAS***. However, tabulations for the daily PRO will include the prorated Pruritus NRS weekly mean for Baseline, Week 1 and Week 2, and weekly value from Week 2 to Week 16, and value every 2 weeks from Week 16 to Week 24 as described in **Table 13**.

A mean plot figure will be created for ***FAS*** using the daily values from Screening period to Week 2, including the mean ± SEM.

Table 13. Analysis Start and End Day For Calculating (Prorated) Pruritus NRS

Week[1]	Start Analysis Day	End Analysis Day	Calculation
W0 (Baseline)	D1 (Baseline) - 7 days	D1 (Baseline) -1 day	Mean of reported values[2]

Week[1]	Start Analysis Day	End Analysis Day	Calculation
W1	D1 (Baseline)	D7	Mean of reported values[2]
W2	D8	D14	Mean of reported values[2]
W3	D15	D21	Single value expected[3]
W4	D22	D28	Single value expected[3]
W5	D29	D35	Single value expected[3]
W6	D36	D42	Single value expected[3]
W7	D43	D49	Single value expected[3]
W8	D50	D56	Single value expected[3]
W9	D57	D63	Single value expected[3]
W10	D64	D70	Single value expected[3]
W11	D71	D77	Single value expected[3]
W12	D78	D84	Single value expected[3]
W13	D85	D91	Single value expected[3]
W14	D92	D98	Single value expected[3]
W15	D99	D105	Single value expected[3]
W16	D106	D112	Single value expected[3]
W18	D113	D126	Single value expected[3]
W20	D127	D140	Single value expected[3]
W22	D141	D154	Single value expected[3]
W24	D155	D168	Single value expected[3]

[1]. ePROs do not have directly a mapped week, therefore, week derivation is performed afterwards. The "week" reference in the table is the range of days the assessment(s) was performed.

[2]. At least 4 out of 7 daily values are required for Baseline visit. However, only 1 value is required after that.

[3]. If more than 1 value is reported within the analysis window mean value will be calculated.

We will follow the following rules for the derivation of the prorated Pruritus NRS weekly mean:

- If multiple assessments on a single day are present, use the first assessment.
- If at least 1 of the 7 days contains non-missing daily assessments, the post-baseline weekly score will be calculated using a prorated weekly average.
- If the range of 7 days are all missing daily assessments, then the weekly score is missing.

The following analyses will be summarised and provided in listings for ***FAS***:

- Percentage of patients with Pruritus NRS ≥4 at baseline achieving Pruritus NRS score ≤4 by visit.
- Percentage of patients with Pruritus NRS ≥4 at baseline achieving ≥4-point improvement in Pruritus NRS from baseline by visit.
- Percentage change in Pruritus NRS score from baseline by week.

12.6.5.2 Dermatology Life Quality Index and Children's Dermatology Life Quality Index

The DLQI is a 10-item validated questionnaire completed by the patient or caregiver used to assess the impact of skin disease on the patient's QoL during the previous week (Finlay & Khan, 1994). The 10 questions are included in **Table 14**. Each question is scored from 0 to 3 ("not at all," "a little," "a lot," and "very much"), giving a total score ranging from 0 to 30. A high score is indicative of a poor QoL.

Adolescents younger than age of 16 years will use the cDLQI, which is based on 10 questions different from those of the DLQI (Finlay & Khan, 1994). The cDLQI questions are also included in **Table 14**.

Both DLQI and cDLQI responses will be captured using an eDiary, as outlined in **Table 1** for each visit.

Note that DLQI/cDLQI score of 1 unanswered question is 0. If the score of 2 or more questions are missing, the total score will be set to missing. For the DLQI, the second part of Question 7 could be a valid missing given that the first part is answered "Yes". Therefore, Question 7 should be considered as one question.

Table 14. Topics and Questions For DLQI and cDLQI

DLQI[1]	cDLQI[2]
1. Symptoms-Itch Over the last week, how itchy, sore, painful or stinging has your skin been?	**1. Symptoms-Itch** Over the last week, how itchy, "scratchy", sore or painful has your skin been?
2. Embarrassment Over the last week, how embarrassed or self-conscious have you been because of your skin?	**2. Embarrassment** Over the last week, how embarrassed or self-conscious, upset or sad have you been because of your skin?
3. Shopping/home/garden[3] Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	**3. Friendships** Over the last week, how much has your skin affected your friendships?
4. Clothes[3] Over the last week, how much has your skin influenced the clothes you wear?	**4. Clothes/shoes** Over the last week, how much have you changed or worn different or special clothes/shoes because of your skin?
5. Social/leisure[3] Over the last week, how much has your skin affected any social or leisure activities?	**5. Leisure/hobbies** Over the last week, how much has your skin trouble affected going out, playing, or doing hobbies?
6. Sports[3] Over the last week, how much has your skin made it difficult for you to do any sport?	**6. Swimming/sports** Over the last week, how much have you avoided swimming or other sports because of your skin trouble?
7. Work/study[3] Over the last week, has your skin prevented you from working or studying? (**Options** include "Yes" or "No") If "No", over the last week how much has your skin been a problem at work or studying? (**Options** do not include "Very much", so, scored 0 to 2)	**7. School/holidays** If school time[4]: Over the last week, how much did your skin problem affect your school work? If holiday time: How much over the last week, has your skin problem interfered with your enjoyment of the holiday?

DLQI[1]	cDLQI[2]
8. Partner/close friends/relatives[3] Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	**8. Teasing/bullying** Over the last week, how much trouble have you had because of your skin with other people calling you names, teasing, bullying, asking questions or avoiding you?
9. Sexual difficulties[3] Over the last week, how much has your skin caused any sexual difficulties?	**9. Sleep** Over the last week, how much has your sleep been affected by your skin problem?
10. Treatment[3] Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	**10. Treatment** Over the last week, how much of a problem has the treatment for your skin been?

Notes:
[1], Options include "Very much"; "A lot"; "A little", or "Not at all" unless stated otherwise.
[2], Options include "Very much"; "Quite a lot"; "Only a little", or "Not at all" unless stated otherwise.
[3], Has an additional option "Not relevant". In this case it will be scored as 0.
[4], Has an additional option "Prevented school" for school time which is scored with a value of 3 like "Very much".

The following endpoints will be assessed and included in tables, and provided in listings for ***FAS***:

- Change in DLQI/cDLQI from baseline by visit.
- Percentage of patients achieving DLQI 0-1 by visit.
- Percentage of patients with DLQI >5 at baseline achieving DLQI ≤5 by visit.
- Percentage of patients with DLQI ≥4 at baseline achieving ≥4-point improvement in DLQI from baseline by visit.
- Percentage of patients achieving cDLQI 0-1 by visit.
- Percentage of patients with cDLQI >5 at baseline achieving cDLQI ≤5 by visit.
- Percentage of patients with cDLQI ≥6 at baseline achieving ≥6-point improvement in cDLQI from baseline by visit.

12.6.5.3 Sleep-Loss Scale

Sleep loss will be assessed by all patients using a PRO instrument. Patients (and if applicable, with help of parents/caregiver if required) will rate their sleep loss on a 5-point Likert scale (with scores ranging from 0 [not at all] to 4 [unable to sleep at all]). Assessments will be recorded by the patient using an eDiary daily up to Week 2, weekly from Week 2 to Week 16, and every 4 weeks from Week 16 to Week 24.

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

As the Sleep-Loss Scale score consists of a daily, prorated weekly and Q4W PRO, all these values will be provided in listings for ***FAS***. However, tabulations for the daily PRO will include the prorated Sleep-Loss Scale score weekly mean for Baseline, Week 1 and Week 2, and weekly value from Week 2 to Week 16, and value every 4 weeks from Week 16 to Week 24 as described in Table 15.

A stacked bar chart of percentage of patients scoring 0 to 4 will be created for ***FAS*** using the daily values from Screening period to Week 2, including the frequencies for each Sleep-Loss Scale score category.

Table 15. Analysis Start and End Day For Calculating (Prorated) Sleep-Loss Scale

Week[1]	Start Analysis Day	End Analysis Day	Calculation
W0 (Baseline)	D1 (Baseline) - 7 days	D1 (Baseline) -1 day	Mean of reported values[2]
W1	D1 (Baseline)	D7	Mean of reported values[2]
W2	D8	D14	Mean of reported values[2]
W3	D15	D21	Single value expected[3]
W4	D22	D28	Single value expected[3]
W5	D29	D35	Single value expected[3]
W6	D36	D42	Single value expected[3]
W7	D43	D49	Single value expected[3]
W8	D50	D56	Single value expected[3]
W9	D57	D63	Single value expected[3]
W10	D64	D70	Single value expected[3]
W11	D71	D77	Single value expected[3]
W12	D78	D84	Single value expected[3]
W13	D85	D91	Single value expected[3]
W14	D92	D98	Single value expected[3]
W15	D99	D105	Single value expected[3]
W16	D106	D112	Single value expected[3]
W20	D113	D140	Single value expected[3]
W24	D141	D168	Single value expected[3]

[1]. ePROs do not have directly a mapped week, therefore, week derivation is performed afterwards. The "week" reference in the table is the range of days the assessment(s) was performed.

[2]. At least 4 out of 7 daily values are required for Baseline visit. However, only 1 value is required after that.

[3]. If more than 1 value is reported within the analysis window mean value will be calculated.

We will follow the following rules for the derivation of the prorated Sleep-Loss Scale score weekly mean:

- If multiple assessments on a single day are present, use the first assessment.
- If at least 1 of the 7 days contains non-missing daily assessments, the post-baseline weekly score will be calculated using a prorated weekly average.
- If the range of 7 days are all missing daily assessments, then the weekly score is missing.

The following analyses will be summarised and provided in listings for ***FAS***:

- Percentage of patients with a Sleep-Loss Scale of ≥2 points at baseline who achieve at least 2-point reduction from baseline by visit.
- Change in Sleep-Loss Scale from baseline by week.

12.6.5.4 Patient-Oriented Eczema Measure

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

Important notes mentioned in the eDiary form are:

- 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.

The total score range and corresponding levels for POEM are:

0-2: Clear or almost clear	**3-7**: Mild eczema	**8-16**: Moderate eczema	**17-24**: Severe eczema	**25-28**: Very severe eczema

The following endpoints will be assessed for the study, summarised and provided in listings for ***FAS***:

- Percentage of patients with POEM ≥4 at baseline achieving ≥4-point improvement in POEM from baseline by visit.
- Percentage change in POEM from baseline by visit.

CCI

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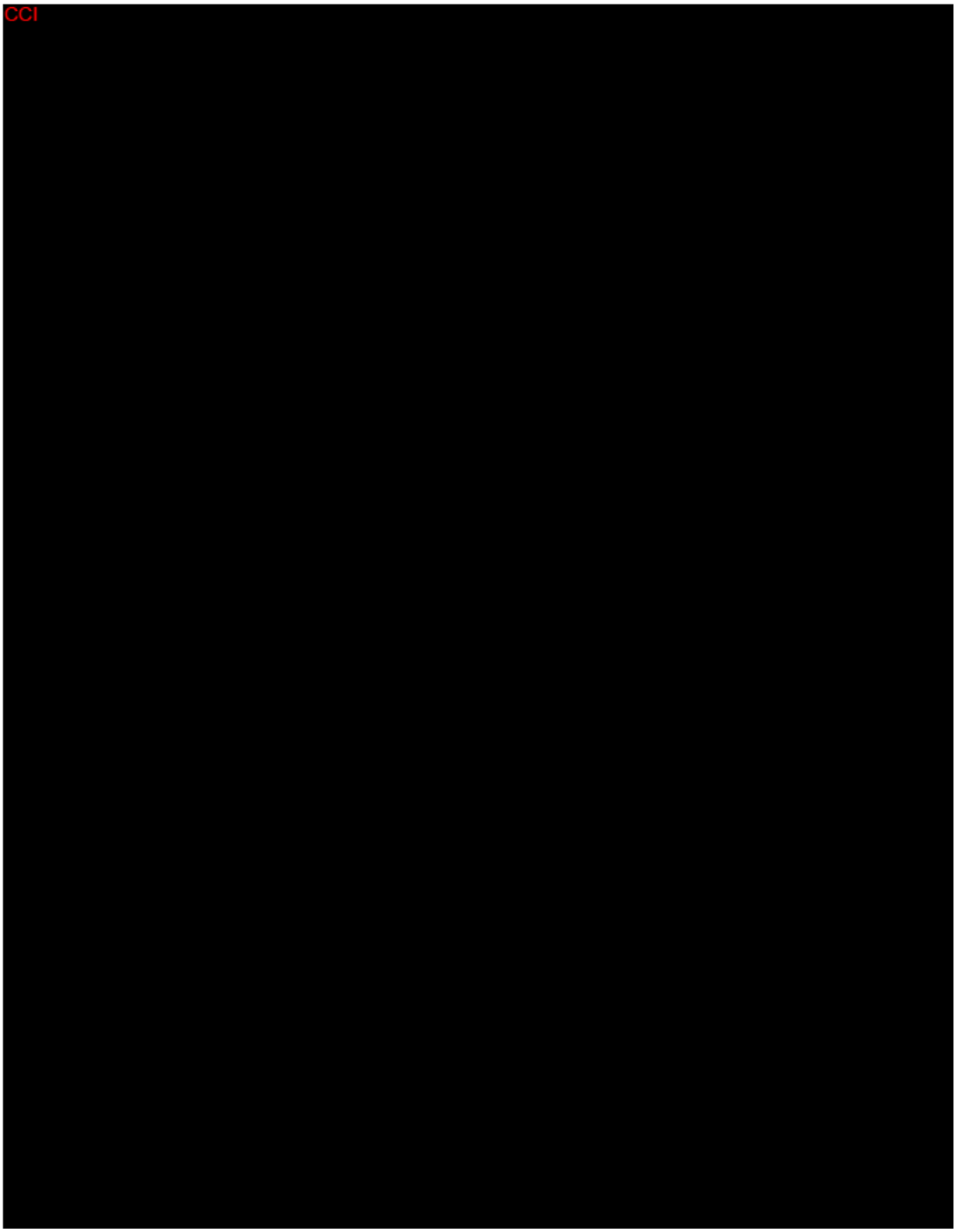

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[redacted]

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12.6.6 Sensitivity Analyses for Effectiveness Analysis

No sensitivity analyses are identified so far.

12.6.7 Supplementary Analyses for Effectiveness Analysis

The following subgroup descriptive analyses will be performed for selected secondary effectiveness endpoints (i.e. percentage of patients achieving EASI Score ≤7, ≤5 and ≤3; percentage of patients achieving EASI 50, EASI 75 and EASI 90; IGA and Face IGA 0/1 and a reduction of ≥2 points from baseline) and both for the primary and supportive estimand:

1. **Prior exposure to Dupilumab**: Yes; No.
2. **Baseline disease severity**: Baseline EASI score ≥ 12 to <16; Baseline EASI score ≥ 16
3. **By Country**: Germany; the Netherlands; the United Kingdom.
4. **Age Group**: Adolescents (12 to <18 years); Adults (≥ 18 years)
5. **Sex**: Male; Female.

Note that no imputation will be made for those subgroup analyses and selection of subgroups will be done based on the imputed datasets for each respective endpoint.

No other *a priori* supplementary analysis will be included. However, *ad hoc* supplementary analysis may be proposed after the IA. As previously described, any SAP amendment following final approved version (v1.0) will be documented in **Section** 2.0. However, this will not apply in case of adding new subgroup analyses.

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[redacted]

12.7 Safety Analyses

All safety analyses will be presented for the ***SAF*** unless stated otherwise.

AEs that started on or after informed consent date and up to and including 30 days after the end of study date will be presented for the analysis. Any adverse events starting outside of this window will not be part of the tabulations and will only be reported in listing.

12.7.1 Safety Endpoint

The safety endpoint is the percentage of patients with TEAEs including SAEs, related AEs, and AEs leading to study treatment discontinuation, and AESIs.

The percentage of patients reporting TEAEs and each AE subtype during the study will be determined using the ***SAF*** as follows:

$$\frac{Number\ of\ patients\ reporting\ TEAEs}{Number\ of\ patients\ in\ the\ SAF}$$

This will be included in a table for overall TEAEs and for each SOC and PT for which there has been at least one TEAE identified.

As part of the secondary safety endpoints, incidence will be described using Incidence Rate (per 100 patient-years). Where specified, event summaries will include the **incidence rate (IR)**. This IR will be expressed per 100 patients-years and will be calculated as follows: the number of patients with at least 1 AE during the study, divided by the sum of patient-years for all patients.

$$\textbf{\textit{Incidence Rate}} = \frac{\#\ patients\ with\ \geq 1\ AE\ during\ ADhope\ study}{Total\ 'Patient\ years'at\ risk\ during\ ADhope\ study\ (SAF)}$$

Note that AE is either treatment-emergent SAE, treatment-emergent AESI or TEAE, as appropriate.

IRs per 100 patient-years will be calculated relative to duration at risk (patient-years) and presented together with 2-sided **95% CIs**. IR 95% CI will be calculated assuming that the number of events in a fixed interval of time follows a Poisson distribution.

Hereby, sum of patient-years will be calculated as sum of duration at risk per patient (years) over all patients in the ***SAF***. Duration at risk will be calculated as described in **Section** 12.1. If the patient did not experience the event of interest the date of study discontinuation will be used in the formula instead of start date of event.

Handling of missing dates is described in **Section** 10.12.2.

12.7.2 Adverse Events

A summary of all TEAEs will be presented, including the number of events reported and the number and percentage of patients reporting at least one TEAE. For TEAEs, the following subcategories will be included in the summary table:

- Any TEAE.
- Any TEAE by severity (mild, moderate, severe).
- Any TEAE relatedness to lebrikizumab treatment (thereafter “related”).
- Any related TEAE by maximum severity (mild, moderate, severe).
- Any serious TEAE.
    - Related serious TEAE (For lebrikizumab, all serious related TEAEs are considered Suspected Unexpected Serious Adverse Reaction [SUSAR]).
- Any TEAE of special interest.
    - Related TEAE of special interest.
    - Serious TEAE of special interest.
    - Related serious TEAE (SUSAR) of special interest.
- Any TEAE leading to lebrikizumab discontinuation.
    - Related TEAE leading to lebrikizumab discontinuation.
    - Serious TEAE leading to lebrikizumab discontinuation.
    - Related serious TEAE (SUSAR) leading to lebrikizumab discontinuation.
- Any TEAE leading to study discontinuation.
    - Related TEAE leading to study discontinuation.
    - Serious TEAE leading to study discontinuation.
    - Related serious TEAE (SUSAR) leading to study discontinuation.
- Any TEAE leading to death.
    - Related TEAE leading to death.
    - Serious TEAE leading to death.
    - Related serious TEAE (SUSAR) leading to death.

A breakdown of the number and percentage of patients reporting TEAE will be tabulated by SOC and PT (coded according to the MedDRA dictionary) and maximum severity – in a decreasing order –, where applicable:

- TEAEs by SOC and PT.
- TEAEs by SOC, PT and maximum severity.
- TEAEs by relatedness to lebrikizumab by SOC and PT. This includes: 1) Related; 2) Possibly Related; 3) Unlikely Related; 4) Not Related; and 5) At Least Possibly Related (i.e. Related and Possibly Related).
- Serious TEAEs by SOC and PT.

- TEAEs of special interest by type and PT.
- TEAEs leading to lebrikizumab discontinuation by SOC and PT.
- TEAEs leading to study discontinuation by SOC and PT.
- TEAEs with an outcome of death by SOC and PT.
- TEAEs of safety topics of special interest by sub-category and PT for the following categories:
    - Conjunctivitis and Other Ocular Events
    - Infections
    - Eosinophilia and Eosinophil-related Disorders
    - Hypersensitivity Reactions
    - Injection Site Reactions
    - Malignancies
    - Atopic Dermatitis Exacerbation

Note that counting will be by patient not event, and patients are only counted once within each body system or PT. Therefore, when counting the number of patients with each event, patients with multiple events within a particular body system or PT will be counted under the category of their most drug-related event within that body system or PT.

All AEs recorded in the eCRF will be provided in a listing. Separate listings will be provided with MedDRA SOC and PTs for TEAEs, Serious TEAEs, TEAEs of special interest, TEAEs related to lebrikizumab, TEAEs leading to lebrikizumab discontinuation, TEAEs leading to study discontinuation, TEAEs leading to study interruption, and TEAEs leading to death, and TEAEs of safety topic of special interest.

Listings will also include, as appropriate, the following variables and levels:

- **MedDRA SOC, PT, Verbatim term and AESI type** (Conjunctivitis; Herpes Simplex or Zoster infection; or Parasitic Infections; if appropriate).
- **Date range and duration** (days)
- **If AE is TEAE:** Yes or No
- **Severity**:
    - Mild.
    - Moderate.
    - Severe.
- **Causality (i.e. Related to lebrikizumab):**
    - Not Related (includes ‘Not Related’ and ‘Unlikely Related’)
    - Related (includes ‘Related’ and ‘Possibly Related’
- **Action taken with study treatment**:
    - Drug Withdrawn.
    - Drug Interrupted.
    - Dose Not Changed.
    - Not Applicable.
- **Did the AE cause the patient to be discontinued from the study**: Yes/No.
- **Was a concomitant or additional treatment given due to this AE**: Yes/No.
- **Outcome**:
    - Fatal.
    - Not Recovered/Not Resolved.

  - Recovered/Resolved.
  - Recovered/Resolved with Sequelae.
  - Recovering/Resolving.
  - Unknown.
- **SAE**: Yes/No.
- **SAE criteria**; Yes/No for each below options:
  - Results in death.
  - Life threatening.
  - Results in initial or prolonged hospitalization.
  - Results in disability or permanent damage.
  - Associated with a congenital anomaly or birth defect.
  - Other medically important event not covered by other serious criteria.
- **AESI:** Yes or No.
- **SUSAR:** Yes or No.
- **AE Identification.**

12.7.3 Deaths and Serious Adverse Events

As previously mentioned, separate tables and listings will be provided with MedDRA SOC and PT for both serious TEAEs and TEAEs leading to death respectively. Deaths occurring in the study will be provided in a separate listing in the ***SAF***.

12.7.4 Follow-up of Adverse Events/Serious Adverse Events

Those AEs/SAEs recorded for the Screening Failure patients or that are still present after the last study drug administration for enrolled patients will be followed-up until resolution or until otherwise agreed between the Sponsor and the Investigator.

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

12.7.5 Laboratory Data

Routine laboratory assessments will be analysed at a designated central laboratory. Tests to be performed are detailed in Table 17.

Blood and urine samples for laboratory testing will be collected in appropriate sampling tubes according to the schedule of assessments (Table 1). It is recommended that blood samples be collected after physical examinations measurement, if applicable. ICON Laboratory Services, or its designated Referral Laboratory, will be used to analyse all laboratory data included in this section. Laboratory assessments will be performed to evaluate safety at scheduled time points during the study.

Table 17. Laboratory Testing Parameters

Haematology Panel	Blood Chemistry Panel		
• Hematocrit (HCT) • Hemoglobin (HGB) • Erythrocytes [Red Blood Cells (RBC) count] • Mean Corpuscular Volume (MCV)	**ELECTROLYTES**: • Sodium • Potassium • Chloride • Calcium	**ENZYMES:** • ALT • AST • ALP • GGT	**SUBSTRATES:** • Glucose • Total cholesterol • Triglycerides • Urea

Haematology Panel	Blood Chemistry Panel		
• Mean Corpuscular Haemoglobin (MCH) • Mean Corpuscular Hemoglobin Concentration (MCHC) • Leucocytes (white blood cells count) • Differential blood count (absolute and percentage of neutrophils, lymphocytes, monocytes, eosinophils and basophils) • Thrombocytes (Platelet count)	• Inorganic phosphate	• LDH • CK	• Creatinine • Total bilirubin • Total protein • Albumin • Uric acid • Blood urea nitrogen
Urine Pregnancy Testing Panel			
A serum β-hCG test will be performed in all pre-menopausal women. All pre-menopausal women who are not sterile at screening will also have a urine pregnancy test performed locally according to the schedule in Table 1. Any woman with a confirmed positive pregnancy test during screening is not eligible for study participation. A positive urine pregnancy test during the treatment period of the study requires a serum β-hCG test in order to confirm the result.			

Abbreviations: **β-hCG** = Beta-Human Chorionic Gonadotropin; **ALP** = Alkaline Phosphatase; **ALT** = Alanine Aminotransferase; **AST** = Aspartate Aminotransferase; **CK** = Creatinine Kinase; **GGT** = Gamma-glutamyl Transferase; **LDH** = Lactate Dehydrogenase.

The International System of Units (SI) will be used for laboratory data. Reference ranges (low or high) for each parameter will be indicated by the Central Laboratory. Clinically significant parameters will be also provided.

Any laboratory data values of the form of '< x' (i.e., below the lower limit of quantification) or '> x' (i.e., above the upper limit of quantification) is imputed as '0.95*x' or '1.05*x', respectively, to allow calculations in tables; however, this is displayed as '< x' or '> x' in the listings.

Laboratory values will be summarised including results on the changes from Screening, and listed individually by patient and time point for ***SAF***, which include haematology and biochemistry results by time point. Separate tables will also include the summary of each group of biochemistry parameters (i.e. electrolytes, enzymes and substrates), along with separate listings for these biochemistry parameters. A separate table will include clinically significant post-baseline laboratory results as assessed by the Investigator and reported in the eCRF. A shift table of screening category to maximum post-baseline category will be included for eosinophils, bilirubin and the following liver enzymes: ALT, AST, GGT and ALP. Categories will be: low, normal, high, total and missing except for eosinophils. In this later case, categories will be as follows: normal (<500 per microliter), mild (500 to <1500 per microliter), moderate (1500 to <5000 per microliter), severe (≥5000 per microliter), total or missing.

Finally, a separate tabulation of patients meeting elevated hepatic criteria as per the upper limit of normal (ULN) will be included for ALT, AST, GGT, ALP and bilirubin. This will be created based on maximum screening category (including a total, each range criteria and missing) as follows:

- For ALT and AST individually based on:
  - **3xULN**: screening total; ≤1xULN; >1xULN and <3xULN; ≥3xULN; and missing. Maximum Post-baseline is ≥3xULN.
  - **5xULN**: screening total; ≤1xULN; >1xULN and <3xULN; ≥3xULN and <5xULN; ≥5xULN; and missing. Maximum Post-baseline is ≥5xULN.
  - **10xULN**: screening total; ≤1xULN; >1xULN and <3xULN; ≥3xULN and <5xULN; ≥5xULN and <10xULN; ≥10xULN; and missing. Maximum Post-baseline is ≥10xULN.

- For GGT based on:
    - **2.5xULN**: screening total; ≤1xULN; >1xULN and <2.5xULN; ≥2.5xULN; and missing. Maximum Post-baseline is ≥2.5xULN.
- For Bilirubin and ALP individually based on:
    - **2xULN**: screening total; ≤1xULN; >1xULN and <2xULN; ≥2xULN; and missing. Maximum Post-baseline is ≥2xULN.

A listing of the hematology results will be also provided. Independent listings will be produced for each group of biochemistry parameters.

Haematology and biochemistry assessments will be performed at Screening and at Week 24.

Pregnancy testing results will only be provided in listings for ***SAF***.

12.7.6 Physical Examinations

Physical examinations will include, at a minimum, head, ears, eyes, nose and throat, skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (cm, only at screening) and weight (kg) will also be measured and recorded to allow accurate calculation of BMI.

For each body system, a result (i.e. normal, abnormal or not done) and any abnormal findings will be recorded, along with whether the result is clinically significant (i.e. yes or no) at Screening and Week 24.

Physical examination will be included as part of tables and listings for the ***SAF***. Additional information including whether there is presence of AD on the face and or hands will be included in the listings.

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AD	Atopic Dermatitis
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Classification
BMI	Body Mass Index
BSA	Body Surface Area
cDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ET	Early Termination
GGT	Gamma-glutamyl Transferase
FAS	Full Analysis Set
IA	Interim Analysis
CCI	[redacted]
ICE	Intercurrent Event
ICF	Informed Consent Form
IGA	Investigator Global Assessment
IMP	Investigational Medicinal Product
IR	Incidence Rate
JAK	Janus Kinase
LLT	Lowest Level Term
MCMC-MI	Markov Chain Monte Carlo – Multiple Imputations
MedDRA	Medical Dictionary for Regulatory Activities
mTLSS	Modified Total Lesion Symptom Score
NRS	Numerical Rating Scale

CCI	[redacted]
POEM	Patient-Oriented Eczema Measure
PRO	Patient-Reported Outcome
PSO	Predictivv Study Operations
PT	Preferred Term
Q2W	Every Other Week
Q4W	Every Fourth Week
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SC	Subcutaneous
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of the Mean
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus and activation-regulated chemokine
TCS	Topical Corticosteroids
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
CCI	[redacted]
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organization

List of Tables

15.0 Appendices

15.1 Appendix 1. Strategy for "Close Events"

In case of **consecutive events** with **same Lowest Level Term (LLT*) (close cases**)** we will consider as one unique event using the following strategy:

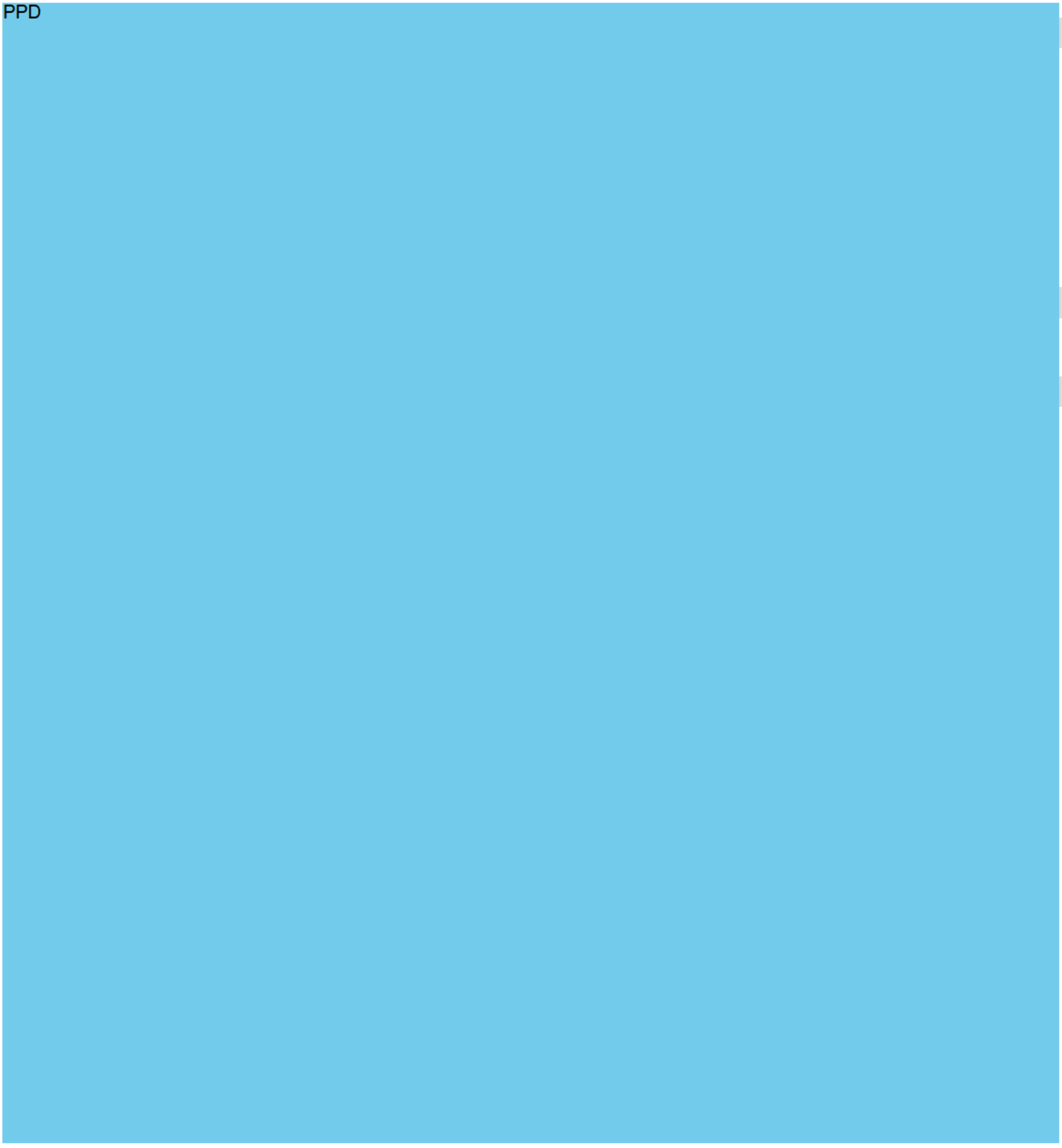
- Merge all consecutive events as one unique event choosing:
  - The maximum **severity** (severe > moderate > mild)
  - The last **outcome** available
    - If events have same start date, then the worst outcome is selected (fatal > not recovered/not resolved > recovered/resolved with sequelae > recovering/resolving > recovered/resolved > unknown)
  - The **serious** one (yes > no)
  - The maximum **relationship** with the drug (related > possibly related > unlikely related > not related)
  - The more restrictive **action taken** (drug withdrawn > drug interrupted > dose not changed > not applicable > unknown)
  - **Start** date:
    - Earliest starting date
  - **End** date:
    - Latest stopping date or ongoing (ongoing > end date)

** Most conservative level.*

*** **Close cases** defined as same LLT consecutive events: end date and start date of the record are the same with a maximum of 1 day gap between events. Examples provided in Table 18.*

Table 18. Illustrative examples for close cases.

AE	Start day	End day	Guidance
1	4	6	1 and 2: This is an overlapping event in terms of LLT and would be concatenated with the start day of 4 and end day of 7.
2	5	7	
3	8	9	3 and 4: Unique in terms of AETERM but duplicated in terms of LLT, needs to be concatenated, even if it is not 'consecutive'.
4	8	9	
5	10	12	5 and 6: Consecutive and they would be concatenated, start day is 10 and end day is 13.
6	12	13	
7	15	17	7 and 8: One day gap between end date of 7 and start date of 8. This would be concatenated with the start day of 15 and end day of 20.
8	18	20	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ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

I understand that my electronic signature is equivalent to my handwritten signature and is therefore legally binding. My electronic signature will remain unique to me and, under no circumstances, am I allowed to disclose my password to any individual which may allow unauthorised access to the system. I understand that I am accountable and responsible for all actions associated with my electronic signature.