STATISTICAL ANALYSIS PLAN

A randomized, double blind placebo-controlled multicenter study of the efficacy and safety of dupilumab in patients with moderate to severe hand eczema refractory to highly potent topical corticosteroids

DUPECZEMAIN

(RC31/18/0269)

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Author	Jonathan Rioual (Biostatistician)

SIGNATURE PAGE

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Study Biostatistician

Signature _____ Date _____

Name: Jonathan Rioual

Study Methodologist

Signature _____ Date _____

Name: Dr. Emilie Bérard

Coordinating Investigator

Signature _____ Date 2024-04-05

Name: Dr. Marie Tauber

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1. MODIFICATION HISTORY

Version	Author	Changes from previous version
1.0	Jonathan Rioual	N/A - First version.
1.1	Jonathan Rioual	Corrected after the March, 28th 2024 meeting with investigators

2. LIST OF ABBREVIATIONS

AE: Adverse Event

ANCOVA: Covariance analysis

ATC1: Anatomical main group

ATC2: Therapeutic subgroup

CHE: Chronic Hand Eczema

CI: Confidence Interval

DLQI: Dermatology Life Quality Index

EASI: Eczema Area and Severity Index

eCRF: electronic Case Report Form

EQ-5D-5L: 5-Levels EQ-5D

HIV: Human Immunodeficiency Virus

IGA: Investigator's Global Assessment

IgE: Immunoglobulin E

ITT: Intention-To-Treat

MCID: Minimal Clinically Important Difference

MedDRA: Medical Dictionary for Regulatory Activities

mTLSS: modified Total Lesion Symptom Score

OLS: Ordinary Least Squares

PaGa: Patient's Global assessment

PP: Per-Protocol

PT: Preferred Term

Q1: 25th percentile

Q3: 75th percentile

SAP: Statistical Analysis Plan

SD: Standard Deviation

SOC: System Organ Class

VAS: Visual Analog Scale

WHODD: World Health Organization Drug Dictionary

3. INTRODUCTION

This Statistical Analysis Plan (SAP) provides a comprehensive and detailed description of the statistical strategy and methods to be used to perform the final analysis of the data for the DUPECZEMAIN study planned to be conducted after the end of the study.

This SAP is based on the protocol version 6.0 dated June 26th, 2023 and on the Clinfile eCRF printed February 02nd, 2024. It was validated before database lock of the study and before the unblinding of the database. Treatment allocation will be provided at the end of the study for all subjects after last subject has completed the study, complete cleaning of database and statistical analysis plan validated.

Further analyses might be conducted based on Health Authority requests or as deemed necessary.

4. STUDY OBJECTIVES

The primary objective of the study is to demonstrate that dupilumab is more effective than placebo for the treatment of patients with moderate to severe chronic hand eczema (CHE) who are resistant or intolerant to highly potent topical corticosteroids as determined by the evolution at week 16 of the modified total lesion symptom score (mTLSS) since baseline.

Secondary objectives are:

- To demonstrate that dupilumab is more effective than placebo to improve pruritus induced by CHE at week 16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to improve pain induced by CHE at week 16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to improve quality of life at week 16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to improve sleep loss induced by CHE at week 16 as compared to baseline.
- To demonstrate that dupilumab is more effective than placebo to induce clearance or almost clearance of CHE at week 16 as defined by the investigator and by the patient.
- To demonstrate that dupilumab is more effective than placebo to improve work productivity at week 16 as compared to baseline.
- To evaluate the efficacy of dupilumab on other parts of the body compared with placebo, in patients with eczema not limited to the hand.
- To evaluate the evolution of laboratory parameters of patients receiving dupilumab compared to those receiving placebo.
- To evaluate the safety of dupilumab as compared to placebo throughout the course of the study.

5. INVESTIGATIONAL PLAN

5.1. OVERALL STUDY DESIGN AND PLAN

The DUPECZEMAIN study is a multicenter (conducted in 4 centers in France), randomized, double-blind, 2-arm parallel-design study comparing dupilumab to a placebo in patients with moderate to severe CHE who are resistant or intolerant to highly potent topical corticosteroids.

The study consists in three phases: screening, treatment phase (16 weeks) and follow-up post treatment (4 weeks).

A patient is eligible for the study (and to start the study treatment) only if complying with all the inclusion/non-inclusion criteria, that is, fulfilling all inclusion criteria without matching any non-inclusion criterion. Inclusion and non-inclusion criteria are checked at the Screening visit, which takes place 1 to 4 weeks before the start of study treatment.
The inclusion criteria are as follows:

- Adult Patients (≥18 years) affiliated to a social insurance protection regimen.
- Patients with moderate to severe chronic (>6 months) hand eczema with an Investigator global assessment (IGA) of 3 or 4 (out of a scale of 0 to 4).
- Patients intolerant (according to the physician) or resistant to highly potent topical corticosteroids. Inadequate response (resistance) to highly potent topical corticosteroids is defined as a history of failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0 [indicating clear] to 2 [indicating mild]) despite treatment with a daily regimen of highly potent topical corticosteroids applied for 14 days or for the maximum duration recommended for highly potent topical corticosteroids.
- Patients who are able to understand the study procedures including the ability to complete patient-oriented questionnaires.
- Patients who are able to apply a stable dose of emollients within 7 days before the baseline visit.
- Patients who agree to sign the written informed consent.

The exclusion criteria are as follows:

- Hypersensitivity to dupilumab or to any of its ingredients.
- Patients under adult autonomy protection system.
- Any other condition (e.g., psoriasis) on the hands that according to the investigator will impair the ability to evaluate treatment effect.
- Treatment with topical corticosteroids or topical calcineurin inhibitors within one week of baseline.
- Treatment with oral immunosuppressants (including cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), alitretinoin or phototherapy within 4 weeks of baseline visit.
- Treatment with an investigational drug within 8 weeks (or 5 half-lives) of baseline.
- Active chronic infection requiring the use of a systemic antibiotic within 2 weeks before study start.
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment.
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.
- Positive for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody at the screening visit.
- Patients with known helminth infections.
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study. Women of childbearing potential who are sexually active and unwilling to use an adequate birth control method.

After confirmation of eligibility, patients are randomly allocated by a computer-generated randomization system in a 1:1 ratio to receive one of the following two treatment strategies:

- Dupilumab 300 mg for subcutaneous administration. Two initial injections of 300 mg dupilumab will be administered, followed by one injection of 300 mg every 2 weeks until week 14.
- Placebo with the same administration procedure.

The randomization is performed in a stratified manner based on the presence or not of a personal history of atopic dermatitis, as it is expected to be the major factor potentially influencing the primary endpoint. Baseline severity is not expected to influence the primary endpoint, as the relative change in mTLSS is not anticipated to be influenced by disease severity.

After randomization, study treatment is begun as soon as possible.

Some treatments/procedures are prohibited during the study as either they may influence disease outcome or may pose a safety risk for patients. Treatment with the following concomitant medications is prohibited during the study

- Treatment with immunomodulating biologics.
- Treatment with an investigational drug (other than dupilumab).
- Treatment with topical corticosteroids or topical calcineurin inhibitors; such agents should not be administered during the study.
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), except if critically medically needed to treat concurrent medical conditions (e.g., asthma).

Study drug will be temporary discontinued (5 half-life before and after vaccination) if a treatment with live (attenuated) vaccine is used through week 16.
In addition, major surgery procedure and phototherapy (medical device or tanning) are prohibited during the 16-week treatment period.
Rescue therapy: if a patient presents with a severe flare of CHE during the course of the study which cannot be managed with emollients and requires intervention, a unique rescue 2-week course of highly potent corticosteroid (betamethasone dipropionate cream) will be administered. The amount of drug used will be recorded. Study treatment will be unchanged.
In contrast, emollients are approved for use in patients during the course of the study. Patients are allowed to take anti-histamines if medically indicated during the study. Patients with comorbid asthma should be on stable treatment. Any change in the dosage of anti-histamines should be captured in the source documents and electronic Case Report Form (eCRF).

The end of the study does correspond to the end of study participation. Patient premature withdrawal from treatment period is mandatory in the following situations: Investigator judgment, Pregnancy or suspected pregnancy, Unacceptable adverse event(s)/serious adverse event(s), Participant decision (wants to discontinue the treatment and agrees to undergo follow-up assessments), Participant withdrawal of consent, Death.

5.2. STUDY ENDPOINTS

5.2.1. Primary endpoint

The primary endpoint measure is percentage change of the severity score mTLSS from baseline to week 16.
The mTLSS combines an evaluation of hand eczema lesions severity including 6 key signs (erythema, desquamation, lichenification/hyperkeratosis, vesiculae, oedema, fissures) and the intensity of pruritus and pain.

5.2.2. Secondary endpoints

Secondary endpoints include the following:

- Evolution of pruritus associated with CHE at week 16 since baseline measured with a visual analog scale (VAS).

- Evolution of pain associated with CHE at week 16 since baseline measured with a visual analog scale.
- Improvement of quality of life at week 16 since baseline measured by Dermatology Life Quality Index (DLQI) (1) and 5-levels EQ-5D (EQ-5D-5L)(2).
- Evolution of sleep loss associated with CHE at week 16 since baseline measured with a VAS.
- Clearance or almost clearance of hand eczema at week 16 as defined by an Investigator's global assessment (IGA)(3) of 0 or 1.
- Clearance or almost clearance of hand eczema at week 16 as assessed by the Patient's global assessment (PaGa)(4) of 0 or 1.
- Improvement of work productivity at week 16 since baseline as assessed by the questionnaire Work Productivity and Activity Impairment (WPAI)(5).
- Evolution of the Eczema Area and Severity Index (EASI) at week 16 since baseline in patients who have eczema on other parts of the body than the hands(6).
- The safety throughout the course of the study (at 20 weeks since baseline) by monitoring adverse events, serious adverse events, injection site reactions.
- Evolution of laboratory parameters (full blood count and total immunoglobulin E (IgE)) at week 16 since baseline.

5.3. DETERMINATION OF SAMPLE SIZE

The sample size is determined by the primary objective of the study, that is, to compare the percentage change in mTLSS score from baseline to Week 16.
His calculations are based on a clinically meaningful absolute difference between groups in the mean percentage change in mTLSS score from baseline to Week 16 of -25% (greater percentage decrease expected in dupilumab compared with placebo). Assuming a standard deviation of 40% in both groups, sample size of 84 patients (42 by group) will achieve over 80% power to detect such a difference with a significance level (type-I error) of 0.05 using a two-sided two-sample t-test (7).
To account for potential non-evaluable patients estimated to 10%, a total of 94 patients will have to be randomized.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. DESCRIPTIVE STATISTICS

Descriptive statistics for quantitative parameters will include the following: number of missing data, number of non-missing observations, mean, Standard Deviation (SD), 25th percentile (Q1), median, 75th percentile (Q3), minimum and maximum values.
Minimum and maximum values will be presented with the same decimal precision as collected. Mean, Q1, median, and Q3, will be displayed with one more decimal place than collected. SD will be displayed with one more decimal place than mean.

Descriptive statistics for qualitative parameters will include the following: number of missing data, number of non-missing observations, counts, and percentages.
Percentages will be calculated on non-missing data, unless otherwise specified (e.g. with imputation of a value according to described rules). Percentages will be displayed with one decimal place.
Of note, for each categorical parameter, all categories specified in the electronic eCRF will be displayed even if there is no observation; in the case there is no observation, result will be displayed as "-" to represent "0 (0.0%)".

This data will be summarized in a table like the one below:

	Placebo arm (N=…)	**Dupilumab arm** (N=…)	**Total** (N=…)
Qualitative parameter			
n/missing	n/na	n/na	n/na
Modality 1	n (%)	n (%)	n (%)
Modality 2	n (%)	n (%)	n (%)
Quantitative parameter			
n/missing	n/na	n/na	n/na
Mean (SD)			
Médian			
p25 ; p75			
Min ; Max			

6.2. INFERENTIAL STATISTICS

The primary objective of study is to demonstrate that dupilumab is more effective than placebo for the treatment of patients with moderate to severe CHE who are resistant or intolerant to highly potent topical corticosteroids as determined by the evolution at week 16 of the mTLSS since baseline. The study is sized on the basis of the primary objective only. The study uses a single primary endpoint and has a confirmatory statistical strategy that pre-specifies just one single null hypothesis relating to the primary endpoint and no formal interim analysis.

The primary analysis of the primary endpoint, which forms the basis for the sample size justification, involves comparing the percentage change from baseline to week 16 of the severity score mTLSS between the experimental arm (dupilumab) and the control arm (Placebo) using a covariance analysis. This analysis includes the group, the stratification factor (personal history of atopy), the baseline mTLSS score and the interaction between the stratification factor and the treatment arm as covariables. The treatment effect is tested at a 5% significance level.
The null hypothesis H_0 is that the percentage change in experimental arm is the same as the percentage change in control arm. The alternative hypothesis H_a is that percentage change in experimental arm differs from percentage change in control arm.

All other analyses of the other efficacy endpoints, are intended to yield supportive evidence related to the primary objective and to provide additional characterization of treatment effects, and no claims are intended. Confidence Intervals (CIs) and statistical tests, if any, that are part of these analyses are of exploratory nature and will be performed without any adjustment of type I error. They will be two-sided and performed each at the 0.05 significance level, unless otherwise specified.

Similarly, analyses on safety endpoints are used in an exploratory manner. CIs and statistical tests, if any, will be two-sided and performed each without any adjustment for multiplicity at the 0.05 significance level.

6.3. GENERAL DATA HANDLING CONVENTIONS

6.3.1. Definition of reference date(s)

Two dates may be used as reference date according to the purpose of the analysis: the date of randomization and the date of first study treatment administration.
In all tables and listings, reference date(s) will be clearly identified.

6.3.2. Calculation of durations and conversion factors

Durations in days are computed as the difference between end and start dates of the assessment under consideration.
The following conversion factors are used to convert days into weeks or months or years, and vice versa:

- 1 week = 7 days.
- 1 month = 30.4375 days.
- 1 year = 365.25 days.

6.3.3. Definition of baseline value/result for safety parameters

Baseline value/result for safety parameters is defined as the last non-missing value/result of the parameter measured prior to the first study treatment administration.

6.3.4. Coding conventions

All medications are coded by Data Management according to World Health Organization Drug Dictionary (WHODD) format B3 version 2018.
All medical and surgical history, as well as all Adverse Events (AEs), are coded by Data Management according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

6.3.5. Handling of missing value for main judgement criteria

About the primary endpoint (percentage change in mTLSS score between visit 0 and visit 9), there are different possibilities depending on the analysis and the visit for which this data is missing:

- If the mTLSS score is completely missing or if more than 25% of items are missing during the first visit,

no imputation will be made and the participants will not be considered in any of the analyses (principal and sensitivity).

- If less than 25% of items are missing, this will be imputed by the value representing the patient's optimal state.
- If the mTLSS score is completely missing or if more than 25% of items are missing at all visits except the first, no imputation will be made and the participants will not be included in any of the analyses (principal and sensitivity).
- If the mTLSS score is completely missing or if more than 25% of items are missing at the visit 9 for less than 10% of randomized patients, no imputation will be performed.
- If the mTLSS score is completely missing or if more than 25% of items are missing at the visit 9 for more than 10% of randomized patients, but this score is entered for at least one visit between visit 2 and visit 8:
    - The last available data will be used for the primary efficacy analysis of the primary endpoint (the last available data per item if less than 25% of items are missing or the last available data for the full score if more than 25% of items are missing).
    - For the first sensitivity analysis, we will conduct multiple imputations, using chained equations (8) with a missing at random assumption, to address missing criteria.
      The imputation model will be carried out by arm in order to take into account possible interaction between the stratum and the arm (9). It will encompass both independent variables and the outcome, along with auxiliary variables predicting missingness and/or associated with the missing variables. Consequently, the imputation model will explicitly include the percentage change in mTLSS, baseline mTLSS and the randomization stratum. In addition to these variables, auxiliary variables will be added to the imputation model. These variables are the most likely to influence the judgement criterion and the possibility of missing data. Thus, the mTLSS scores at intermediate time (visit 3, visit 5 and visit 7) and raw IGA scores from baseline to V9 (scored from 0 to 4) will be added to the imputation model.
    - For the second sensitivity analysis, no imputation will be made and the analysis will be based solely on available data.

6.3.6. Handling of missing value for secondary judgement criteria

For secondary endpoints, all secondary judgement criteria requiring a difference calculation except WPAI (EASI, DLQI, EQVAS of EQ-5D-5L, the several VAS for measuring pruritus, pain or sleep loss, and the laboratory parameters) will be treated as follows:

- If they are completely missing or if more than 25% of items are missing for scores calculated from different assessments (EASI and DLQI) during the first visit, no imputation will be made and the participants will not be considered in any of the analyses.
- For scores calculated from different assessments (EASI and DLQI), if less than 25% of items are missing at the inclusion visit, this will be imputed by the value representing the patient's optimal state.
- If they are completely missing or if more than 25% of items are missing for scores calculated from different assessments (EASI and DLQI) at all visits except the first, no imputation will be made and the participant will not be included in any of the analyses.
- If they are completely missing or if more than 25% of items are missing for scores calculated from different assessments (EASI and DLQI) at the visit 9 for less than 10% of randomized patients, no imputation will be performed.
- If they are completely missing or if more than 25% of items are missing for scores calculated from different assessments (EASI and DLQI) at the visit 9 for more than 10% of randomized patients, but this score is entered for at least one visit between visit 2 and visit 8, the last available data will be used for the analysis of the secondary endpoint.
- For scores calculated from different assessments (EASI and DLQI), if less than 25% of items are missing and this item has been completed for a visit other than the inclusion visit, only the missing item will be imputed using the last available data to complete the score.

The secondary endpoint WPAI will be treated as follows:

- If it is completely missing or if more than 25% of items are missing during the first visit or the visit 9, no

imputation will be made and the participants will not be considered in any of the analyses.
- If less than 25% of items are missing and the missing items are item 1, 2, 3, 5 and/or 6, they will be imputed by the value representing the patient's optimal state.
- If less than 25% of items are missing and item 4 is one of the missing items, it will be imputed by 35 – (result for item 2 + result for item 3) corresponding to statutory working hours in France minus the sum of hours missed. If this value is less than zero, it will be replaced by the value 0.

For qualitative secondary endpoints IGA and PaGa, their treatment will be different:
- If they are missing during all the visits after visit 1, no imputation will be made and the participants will not be considered in any of the analyses.
- If they are missing at the visit 9 for less than 10% of randomized patients, no imputation will be performed.
- If they are missing at the visit 9 for more than 10% of randomized patients, the last available dataset will be used for the analysis of the secondary endpoint.

The secondary qualitative criterion EQ-5D-5L will also be treated differently:
- If it is completely missing or if more than 25% of items are missing during the first visit, no imputation will be made and the participants will not be considered in any of the analyses.
- If less than 25% of items are missing at the inclusion visit, this will be imputed by the value representing the patient's optimal state.
- If it is completely missing or if more than 25% of items are missing during all the visits after visit 1, no imputation will be made and the participants will not be considered in any of the analyses.
- If it is completely missing or if more than 25% of items are missing at the visit 9 for less than 10% of randomized patients, no imputation will be performed.
- If it is completely missing or if more than 25% of items are missing at the visit 9 for more than 10% of randomized patients, the last available dataset will be used for the analysis of the secondary endpoint (the last available data for the items if less than 25% of items are missing or the last available data for the full score if more than 25% of items are missing).

6.3.7. Handling of missing/incomplete dates for birthdate

If the entire date of birth is missing, no imputation is performed. Given that the data collection only involves the month and year of birth, any missing day is assumed to be the 1st.

6.3.8. Handling of missing/incomplete dates for diagnosis of CHE

If the entire date or the year of diagnostic is missing, no imputation is performed. In case of incomplete date with both missing day and month parts, missing day/month is imputed by January 1st. In case of incomplete date only for the day or month, the missing day or month is imputed by 1 representing the first day of the month or the first month of the year (January).

6.3.9. Handling of missing/incomplete dates for visit

If the entire date of visit is missing, no imputation is performed and the visit will be deemed not to have taken place. In case of incomplete date with missing year, day or/and month parts, missing year/day/month is not imputed and this date will be considered as unknown and outside the expected timeframe.

6.3.10. Handling of missing/incomplete dates for adverse events

In case of completely missing or incomplete AE onset date, an imputed AE onset date is calculated in order to derive AE treatment-emergence and AE period-occurrence statuses in any. Always one and the same imputation rule is used, that is, in order not to miss any AEs that occur or may have occurred from the first study treatment administration, imputation rule sets missing/incomplete onset date to the date of the first study treatment administration if another date is not obvious, otherwise "as early as possible" (see details below).

In case of completely missing or incomplete AE end date, an imputed AE end date is derived to help for imputation of missing/incomplete AE onset date, if any, so that inconsistency in the chronology of the dates does not arise (see details below).

Of note, imputed AE onset and end dates are for treatment-emergence/period-occurrence status categorization purpose only; they will neither be used to compute other information on AEs, such as duration, nor be displayed in any individual data listing.

Imputation of AE end date

For AEs that are not "ongoing", as reported by investigators on the adverse event forms, missing/incomplete end dates are handled as follows:

- In case of completely missing end date, missing end date is imputed by the date of the patient's end-of-study derived as the latest date among the date of premature withdrawal from study as reported in the "Early study discontinuation" eCRF form (if any) and the date of last study visit performed.
- In case of incomplete end date with both missing day and month parts, missing end day/month is imputed by 31 December.
- In case of incomplete end date with only missing day part, missing end day is imputed by the last day of the month.

Imputation of AE onset date

Missing/incomplete AE onset dates are handled as follows:

- In case of completely missing onset date:
  - If AE end date (after being imputed as above where necessary) is after or equal to the date of the first study treatment administration, missing onset date is imputed by the date of the first study treatment administration.
  - If AE end date (after being imputed as above where necessary) is prior to the date of the first study treatment administration, missing onset date is imputed by the date of the patient's informed consent signature.
- In case of incomplete onset date with both missing day and month parts:
  - If onset year is the same as the year of the first study treatment administration and AE end date (after being imputed as above where necessary) is after or equal to the date of the first study treatment administration, missing onset day/month is imputed by the day/month part of the first study treatment administration date.
  - If onset year is the same as the year of the first study treatment administration and AE end date (after being imputed as above where necessary) is prior to the date of the first study treatment administration, missing onset day/month is imputed by 01 January.
  - If onset year is prior to the year of the first study treatment administration, missing onset day/month is imputed by 01 January.
  - If onset year is after the year of the first study treatment administration, missing onset day/month is imputed by 01 January.
- In case of incomplete onset date with only missing day part:
  - If onset month/year is the same as the month/year of the first study treatment administration and AE end date (after being imputed as above where necessary) is after or equal to the date of the first study treatment administration, missing onset day is imputed by the day part of the first study treatment.
  - If onset month/year is the same as the month/year of the first study treatment administration and AE end date (after being imputed as above where necessary) is prior to the date of the first study treatment administration, missing onset day is imputed by 01 (first day of the month).
  - If onset month/year is prior to the month/year of the first study treatment administration, missing onset day is imputed by 01 (first day of the month).

- If onset month/year is after the month/year of the first study treatment administration, missing onset day is imputed by 01 (first day of the month).

6.3.11. Handling of missing/incomplete dates for medications

In case of completely missing or incomplete medication start date (respectively end date), an imputed medication start date (respectively end date) is calculated in order to derive a medication prior/concomitant status relative to study treatment in any case. Always one and the same imputation rule is used, that is, imputation rule considers medication as concomitant to study treatment as soon as the non-concomitance is not obvious, setting missing/incomplete start date to the date of the first study treatment administration if another date is not obvious, otherwise "as early as possible", and setting missing/incomplete end date to "as late as possible" (see details below).

Of note, imputed medication start and end dates are for categorization purpose only; they will neither be used to compute information on medications other than prior/concomitant status relative to study treatment, such as duration, nor be displayed in any individual data listing.

Imputation of medication end date

For medications that are not ticked "Ongoing", as reported by investigators on the concomitant medication forms, missing/incomplete end dates are handled as follows:

- In case of completely missing end date, missing end date is imputed by the date of the patient's end-of-study derived as the latest date among the date of premature withdrawal from study as reported in the "Early study discontinuation" eCRF form (if any) and the date of last study visit performed.
- In case of incomplete end date with both missing day and month parts, missing end day/month is imputed by 31 December.
- In case of incomplete end date with only missing day part, missing end day is imputed by the last day of the month.

Imputation of medication start date

Missing/incomplete medication start dates are handled as follows:

- In case of completely missing start date:
  - If medication end date (after being imputed as above where necessary) is after or equal to the date of the first study treatment administration, missing start date is imputed by the date of the first study treatment administration.
  - If medication end date (after being imputed as above where necessary) is prior to the date of the first study treatment administration, missing start date is imputed by the date of the patient's informed consent signature.
- In case of incomplete start date with both missing day and month parts:
  - If start year is the same as the year of the first study treatment administration and medication end date (after being imputed as above where necessary) is after or equal to the date of the first study treatment administration, missing start day/month is imputed by the day/month part of the first study treatment administration date.
  - If start year is the same as the year of the first study treatment administration and medication end date (after being imputed as above where necessary) is prior to the date of the first study treatment administration, missing start day/month is imputed by 01 January.
  - If start year is after or prior to the year of the first study treatment administration, missing start day/month is imputed by 01 January.
- In case of incomplete start date with only missing day part:
  - If start month/year is the same as the month/year of the first study treatment administration and medication end date (after being imputed as above where necessary) is after or equal to the date of the

first study treatment administration, missing start day is imputed by the day part of the first study treatment administration date.

- If start month/year is the same as the month/year of the first study treatment administration and medication end date (after being imputed as above where necessary) is prior to the date of the first study treatment administration, missing start day is imputed by 01 (first day of the month).
- If start month/year is after or prior to the month/year of the first study treatment administration, missing start day is imputed by 01 (first day of the month).

6.4. REPORTING CONVENTIONS

Unless otherwise specified, summary tables by MedDRA System Organ Class (SOC) and Preferred Term (PT) will be sorted on decreasing total frequency of SOC and decreasing total frequency of PT in a given SOC, based on frequency in the pooled data across the arms. In case of equal total frequency, alphabetic order will be used.

Unless otherwise specified, summary tables by WHODD anatomical main group (ATC1) and therapeutic subgroup (ATC2) will be sorted on decreasing total frequency of ATC1 and decreasing total frequency of ATC2 in a given ATC1, based on frequency in the pooled data across the arms. In case of equal total frequency, alphabetic order will be used.

6.5. SOFTWARE DOCUMENTATION

All statistical analyses will be performed using SAS® for Windows version 9.4 or later, and/or STATA® version 18 or later.

7. ANALYSIS POPULATIONS

7.1. ITT POPULATION

The Intention-To-Treat (ITT) population is the set of all randomized patients, that is, all patients who were randomly assigned to one of the two arms of the study (Control arm, experimental arm) by the randomization system.

The ITT population will be used as the primary set of patients for the efficacy analysis - in particular the primary analysis of the primary endpoint will be carried out on the ITT population.
Analyses by arm carried out on the ITT population will be done on the basis of the intention-to-treat principle, that is, patients will be analyzed as members of the arm they were randomly assigned by the randomization system.

7.2. PP POPULATION

The Per-Protocol (PP) population consists of patients from the ITT population who are assessable for the primary endpoint and are deemed not to have major protocol deviations.

Patients will be analyzed as members of the arm corresponding to the study treatment they actually received - that is, as soon as a patient receives dupilumab as part of study, he/she will be analyzed in dupilumab Arm ; on the contrary, a patient who never receives dupilumab as part of study, will be analyzed in placebo Arm.

The PP population will be used as a supportive set of patients for the efficacy analysis to investigate the sensitivity of the conclusions drawn from the analyses of the primary endpoint carried out on the ITT population.

7.3. TREATED POPULATION

The Treated population is the set of all randomized patients who received at least one administration of the study treatment (dupilumab or placebo). The Treated population will be used as the primary set of patients for the safety analysis.

Analyses by arm carried out on the Treated population will be done on the basis of the as-treated principle, that is, patients will be analyzed as members of the arm corresponding to the study treatment they actually received - that is, as soon as a patient receives dupilumab as part of study, he/she will be analyzed in dupilumab Arm ; on the contrary, a patient who never receives dupilumab as part of study, will be analyzed in placebo Arm.

8. PROTOCOL DEVIATIONS AND EXCLUSIONS FROM EFFICACY ANALYSES

8.1. PROTOCOL DEVIATIONS

Protocol deviations may be significant contributors to analysis bias. The following criteria are considered to be the most relevant for measuring the non-compliance to the protocol that may have an impact on the results of the analyses:

- Lack of compliance to entry criteria:
  - Failure to satisfy inclusion criteria.
    Determination of the non-compliance will be done by combining programming and medical review, using investigator "Yes/No" answers to inclusion criteria as well as other inclusion criterion-related data as much as possible.
  - Failure to satisfy non-inclusion criteria.
    Determination of the non-compliance will be done by combining programming and medical review, using investigator "Yes/No" answers to non-inclusion criteria as well as other non-inclusion criterion-related data as much as possible.
- Randomization irregularities:
  - Randomization in wrong stratum; that is, randomization performed based on erroneous data (investigator data entry) that have led to erroneous level for the stratification of the randomization. Determination of the non-compliance will be done by programming using randomization data from the randomization system as well as data related to the gathering of information about the disease history.
  - Non-compliance with the randomization schedule; that is, arm allocation not following the sequential order of the underlying stratified permuted block design.
    Determination of the non-compliance will be done by programming using data from the randomization and data from the randomization schedule.
- Dosing irregularities:
  - No intake of study treatment while randomized.
    Determination of the non-compliance will be done by programming using data related to study treatment administrations.
  - Intake of study treatment not corresponding to study treatment randomly assigned to by the randomization system; that is, receiving a placebo when randomized to dupilumab Arm, or receiving dupilumab when randomized to placebo Arm.
    Determination of the non-compliance will be done by programming using data related to study treatment administrations and data related to randomization.
  - Poor compliance to dupilumab treatment; that is, administration of more or less than 9 injections (18ml/2700mg) during the different study visits. Determination of the non-compliance will be done by programming using data related to study treatment administrations.
  - Poor compliance to placebo treatment; that is, administration of more or less than 9 injections (18ml) during the different study visits. Determination of the non-compliance will be done by programming using data related to study treatment administrations.
- Irregularities in time between visit/injection dates:
  - Scheduled visit/injection dates vary by plus or minus 3 days from the expected date.
    Determination of the non-compliance will be done by programming using data related to visit/injection dates.
  - The scheduled date for visit at V9 (16 weeks from the date of randomization (V1)) differs by plus or minus 24 days from the expected date.
    Determination of the non-compliance will be done by programming using data related to the V1 date and the V9 date.

- Lack of efficacy measurements:
  - No primary endpoint assessment; that is, no mTLSS score at week 16 available.
    Determination of the lack of efficacy measurements will be done by programming using data related to mTLSS assessments.
- Concomitant therapy/medication restrictions not followed:
  - Intake of non-protocol therapy during the study; that is, intake, between day of randomization (included) and day of assessment to week 16 of mTLSS. Non-protocol therapies prohibited during the study are:
    - Treatment with immunomodulating biologics
    - Treatment with an investigational drug (other than dupilumab)
    - Treatment with topical corticosteroids or topical calcineurin inhibitors; such agents should not be administered during the study.
    - Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), except if critically medically needed to treat concurrent medical conditions (e.g., asthma).

    Study drug will be temporary discontinued (5 half-life before and after vaccination) if a treatment with live (attenuated) vaccine is used through week 16.

    In addition, major surgery procedure and phototherapy (medical device or tanning) are prohibited during the 16-week treatment period.

    Rescue therapy: if a patient presents with a severe flare of CHE during the course of the study which cannot be managed with emollients and requires intervention, a unique rescue 2-week course of highly potent corticosteroid (betamethasone dipropionate cream) will be administered. The amount of drug used will be recorded. Study treatment will be unchanged.

    Determination of the non-compliance will be done by combining programming and medical review, using medication data.

8.2. EXCLUSIONS FROM EFFICACY ANALYSES

8.2.1. Exclusions from the ITT population

There is no exclusion from the ITT population (primary set of patients for the efficacy analysis), all randomized patients being included in the ITT population.

8.2.2. Exclusions from the PP population

Criteria for a randomized patient to be excluded from the PP population are those major criteria of non-adherence to study protocol, that may be likely to affect the assessment of the primary endpoint. These criteria are as follows:

- Patients who are not evaluable for primary endpoint
- Patients who do not meet the diagnosis criteria for hand dermatitis
- Patients with only mild disease at baseline (IGA<3)
- Patients with a treatment dose not in line with the expected dose (9 injections)
- Time difference between V1 and V9 not included between ± 24 days compared to the expected duration
- Patients using systemic immunosuppressant, including oral corticosteroids, through week 16
- Patients with a severe flare of CHE using highly potent corticosteroid (betamethasone dipropionate cream) as rescue therapy for more than 2-week, through week 16.

Inhaled/nasal corticosteroid for asthma, rhinitis or chronic obstructive pulmonary disease will be considered as authorized treatment.
Intra articular corticosteroid injection and topical corticosteroids not applied to the hands will be considered

as minor protocol violation.

Patients with a major protocol violation will be listed during the Blind Review.

Number and percentage of patients excluded from the PP population will be summarized overall and by exclusion criterion on the ITT population. Results will be provided on the pooled data across the two arms and by arm.

Tabulated individual data listing will be provided for those patients excluded from the PP population; listing will include the reason(s) for being excluded from the PP population.

9. DISPOSITION OF PATIENTS AND PATIENT WITHDRAWAL

9.1. DISPOSITION OF PATIENTS

A patient is defined as "screened" if he/she has signed the informed consent and has provided demographic and/or baseline screening assessments, regardless of his/her randomization and treatment status in the study.

A patient is defined as "randomized" if he/she was randomly assigned to one of the two arms of the study (Arm A, Arm B) by the randomization system.

A patient is defined as "treated" if he/she received at least one administration of study treatment regardless of the agent administered (dupilumab or placebo as part of the study treatment) and of the amount administered.

Total number of patients will be provided for the following sets of patients:

- All screened patients.
- All non-randomized patients; overall and by reason for not being randomized (of note, a patient can be counted in more than one reason).
- All randomized patients; overall and by arm being randomly assigned to by the randomization system.
- All randomized patients who were treated; overall and by arm being randomly assigned to by the randomization system.

Tabulated individual data listings will be provided for the following sets of patients:

- All non-randomized patients; listing will include the reason(s) for not being randomized.
- All randomized patients who did not receive study treatment; listing will include arm as randomly assigned to by the randomization system and the reason(s) for not receiving study treatment.

Number of patients in each analysis population as defined in Section 7 will be summarized overall and by arm. ITT population and PP population will be further summarized using counts and percentages by those factors used for the stratification of the randomization. Results will be provided on the pooled data across the two arms and by arm. Levels of factors will be derived from actual data - that is, last investigator eCRF data entry - to compensate for cases where erroneous stratification factor information were given at the time of randomization leading to randomization in a wrong stratum.

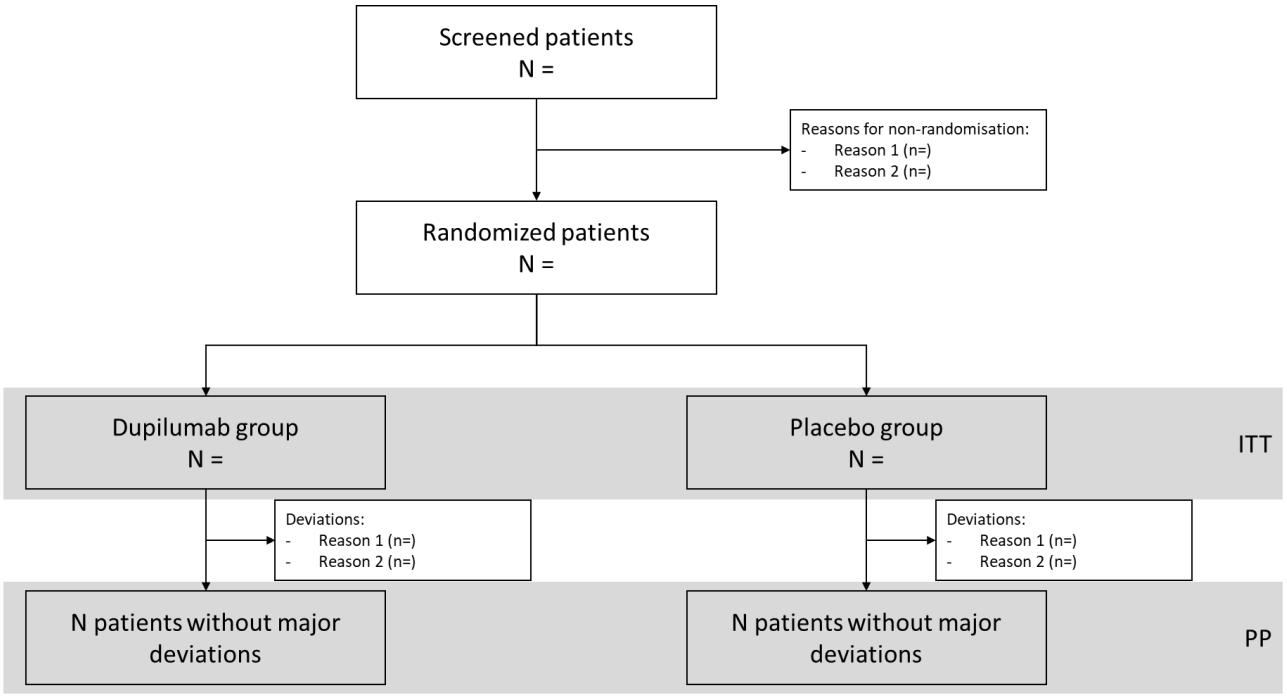
9.2. PATIENT WITHDRAWAL

A patient is derived as having prematurely discontinued the study if investigator "Yes/No" answer to question "Has the patient prematurely discontinued the study?" on the "Early study discontinuation" eCRF form is "Yes", and the reason for premature discontinuation is that as reported by the investigator.

Number and percentage of patients who prematurely discontinued the study will be summarized on the ITT population, on the Treated population, and on the PP population, overall and by reason for premature discontinuation. Results will be provided on the pooled data across the two arms and by arm.

9.3. FLOW CHART

To summarize this information, a flow chart will be produced. It will take the following form:


Screened patients
N =
Reasons for non-randomisation:
- Reason 1 (n=)
- Reason 2 (n=)
Randomized patients
N =
Dupilumab group
N =
Placebo group
N =
ITT
Deviations:
- Reason 1 (n=)
- Reason 2 (n=)
Deviations:
- Reason 1 (n=)
- Reason 2 (n=)
N patients without major deviations
N patients without major deviations
PP

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Analyses will be carried out on the ITT population, in a descriptive manner, using appropriate statistics as described in Section 6.1. Results will be provided on the pooled data across the two arms and by arm.
If the ITT population and the PP population differ by more than 10% (that is, if more than 10% of patients in the ITT population are finally excluded from the PP population), the analyses will be further carried out on the PP population.
These results will also be presented in the appendix for patients of the optional sub-study who had a biopsy at V1 and for patients of the optional sub-study who had a biopsy at V9. These results will be provided based on the pooled data across the two arms and by arm.

Number and percentage of patients with and without each eligibility criterion will be provided on the pooled data across the two arms and by arm.

10.1. DEMOGRAPHIC CHARACTERISTICS

- Gender (qualitative parameter: “Male”, “Female”)
- Age in years (quantitative parameter) calculated at patient’s inclusion as follows: $\frac{\text{Date of randomization - Date of birth}}{365.25}$ rounded to the nearest lower integer.
- Phototype (qualitative parameter: “1”, “2”, “3”, “4”, “5”, “6”)
- Profession (qualitative parameter: “Nursing staff”, “Cleaning, maintenance housekeeping, personal assistance”, “Hairdresser”; “Beautician”, “Retired”, “Public works”, “Other”)
- Working test (qualitative parameter: “Positive”, “Negative”, “Doubtful”, “Not applicable”)
- Aggravating factors of occupational (qualitative parameter: “Yes”, “No”)
    - If “Yes”, of an irritant nature? (qualitative parameter: “Yes”, “No”)
        - Please describe (qualitative parameter in plain terms)
    - If “Yes”, of an allergic nature? (qualitative parameter: “Yes”, “No”)
        - Please describe (qualitative parameter in plain terms)
        - Contact allergy confirmed by allergological tests? (qualitative parameter: “Yes”, “No”)
- Aggravating factors at home and/or leisure activities (qualitative parameter: “Yes”, “No”)
    - If “Yes”, of an irritant nature? (qualitative parameter: “Yes”, “No”)
        - Please describe (qualitative parameter in plain terms)
    - If “Yes”, of an allergic nature? (qualitative parameter: “Yes”, “No”)
        - Please describe (qualitative parameter in plain terms)

10.2. HISTORY OF THE DISEASE

- Time since diagnosis of CHE (quantitative parameter) calculated at patient’s inclusion as follows: $\frac{\text{Date of inclusion - Date of diagnosis of CHE}}{365.25}$ rounded to one decimal place.
- Previous treatments for CHE:
    - Ciclosporin (qualitative parameter: “Yes”, “No”)
        - If “Yes”, duration in months (quantitative parameter)
    - Methotrexate (qualitative parameter: “Yes”, “No”)
        - If “Yes”, duration in months (quantitative parameter)
    - Alitretinoine (qualitative parameter: “Yes”, “No”)
        - If “Yes”, duration in months (quantitative parameter)
    - Oral corticosteroid (qualitative parameter: “Yes”, “No”)

        - If "Yes", duration in months (quantitative parameter)
    - Phototherapy (qualitative parameter: "Yes", "No")
        - If "Yes", type (qualitative parameter in plain terms)
        - If "Yes", number of sessions (quantitative parameter)
    - Powerful or very powerful dermocorticoids (qualitative parameter: "Yes", "No")
    - Topical tacrolimus (qualitative parameter: "Yes", "No")
- Time off work in connection with CHE? (qualitative parameter: "Yes", "No")
- Therapeutic education session for CHE already completed? (qualitative parameter: "Yes", "No")
- History of atopy
    - History of personal atopy (qualitative parameter: "Yes", "No")
    - Atopic dermatitis (qualitative parameter: "Yes", "No")
    - Allergic rhinitis (qualitative parameter: "Yes", "No")
        - If "Yes", (qualitative parameter: "Intermittent", "Mild persistent", "Severe persistent")
    - Asthma (qualitative parameter: "Yes", "No")
        - If "Yes", (qualitative parameter: "Intermittent", "Mild persistent", "Moderate persistent", "Severe persistent")
    - Allergic conjunctivitis (qualitative parameter: "Yes", "No")
    - Family history of atopy (qualitative parameter: "Yes", "No")
    - Currently off work due to CHE? (qualitative parameter: "Yes", "No")
        - If yes, duration in months (quantitative parameter)

10.3. BIOLOGICAL CHECK-UP

- Hemoglobin in g/dL (quantitative parameter)
- Platelets in G/L (quantitative parameter)
- Leukocytes in G/L (quantitative parameter)
- Eosinophilic polymorphs in G/L (quantitative parameter)
- Hepatitis B serology (qualitative parameter: "Positive", "Negative", "Hepatitis B cured", "Vaccination status")
- Hepatitis C serology (qualitative parameter: "Positive", "Negative")
- HIV serology (qualitative parameter: "Positive", "Negative")
- Total IgE
    - Sample taken (qualitative parameter: "Yes", "No")
        - If "No", why? (qualitative parameter in plain terms)
    - Result in kUI/L (quantitative parameter)

10.4. ALLERGY ASSESSMENT

- Known sensitization to pneumallergens (qualitative parameter: "Yes", "No")
    - If "Yes, the answer "Yes" or "No" (qualitative parameter) is expected for the following pneumallergens: DP/DF mites, Cockroach (native), Cat, Dog, Grass, Plantain, Parietaria, Mugwort, Ragweed, Alternaria, Aspergillus, Latex(native), Birch, Olive, Plane tree, Cypress, Type of allergen(s) unknown to the patient
- Food allergies (qualitative parameter: "Yes", "No")
    - If "Yes, the answer "Yes" or "No" (qualitative parameters) is expected for anaphylaxis, oral syndrome and eviction regarding various food. The answer "No", "Partial" or "Complete" is expected for tolerance. The food concerned are: Egg white, Fish, Shrimp, Cow's milk, Celery, Apple, Peach, Peanut, Kiwifruit, Hazelnut, Nuts, Sesame, Wheat, Soya, Cashew nuts, Other.
- Other allergies: Contact allergy suspected on examination? (qualitative parameter: "Yes", "No")
- Allergological tests carried out? (qualitative parameter: "Yes", "No")
    - If "Yes", the following positive patch tests will be ticked off (qualitative parameters): None,

Potassium dichromate, P-Phenylenediamine, Thiuram-mix, Neomycin Cobalt chloride, Benzocaine, Nickel sulphate, Clioquinol, Colophonium, Paraben Mix (Butyl, ethyl, methyl, proppyl Paraben), N'Isopropylphenylenediamine, LANOLIN, Mercapto Mix, Epoxy resin, Bisphenol A , Peru Balsam (MYROXYLON PERERAE), 4-tert-Butylphenoformaldehyde resin, Mercaptobenzothiazole, FORMALDEHYDE, Fragrance mix 1, Sesquiterpene Lactone Mix, Quaternium 15, 2-Methoxy-6-n-pentyl-4-benzoquinone (Primine), Methylchloroisothiazolinone (AND) Methyl Isothiazolinone, Budesonide, Tixocortol-21-Pivalate, Methyldibromo Glutaronitrile, Fragrance mix 2, Hydroxymethylpentylcyclohenecarboxaldehyde, Methyl Isothiazolinone at 2000 ppm WATER, Textile Dye mix, Hydrocortisone-17-Butyrate, 3-(Dimethylamino)-1-Propylamine (DMAPA), Amerchol, Benzalkonium Chloride 0. 1% water, Limonene Hydroperoxide, Laurylglucoside, Benzyl Alcohol (Benzyl Alcohol), Linalool Hydroperoxide, Iodopropynyl Butylcarbamate, 2-n-Octyl-4 Isothiazolin-3-one (octylisothiazolinone), Decylglucoside, Other.

- If “Other”, specify (qualitative parameter in plain terms)

10.5. CLINICAL EXAMINATION

10.5.1. Clinical examination

- Weight in kg (quantitative parameter)
- Height in cm (quantitative parameter)
- SBP (systolic blood pressure) in mmHg (quantitative parameter)
- DBP (diastolic blood pressure) in mmHg (quantitative parameter)
- Pulse in bpm (quantitative parameter)
- Temperature in °C (quantitative parameter)

10.5.2. Ocular symptoms

- Ocular symptoms (qualitative parameter: “Yes”, “No”)
- If “Yes”,
    - Tearing (qualitative parameter: “Yes”, “No”)
    - Tingling, foreign body sensation (qualitative parameter: “Yes”, “No”)
    - Pruritus (qualitative parameter: “Yes”, “No”)
    - Dry syndrome (qualitative parameter: “Yes”, “No”)
    - Eye burns (qualitative parameter: “Yes”, “No”)
    - Does the patient have a red eye on clinical examination? (qualitative parameter: “Yes”, “No”)
    - Eye involved (qualitative parameter: “Right”, “Left”, “Both eyes”)
    - Has the patient had an initial ophthalmological examination? (qualitative parameter: “Yes”, “No”)

11. DISEASE ASSESSMENT

Analyses will be carried out on the ITT population, in a descriptive manner, using appropriate statistics as described in Section 6.1. Results will be provided on the pooled data across the two arms and by arm.
If the ITT population and the PP population differ by more than 10% (that is, if more than 10% of patients in the ITT population are finally excluded from the PP population), the analyses will be further carried out on the PP population.
These results will also be presented at baseline and at visit 9 in the appendix for patients of the optional sub-study who had a biopsy at V1 and for patients of the optional sub-study who had a biopsy at V9. These results will be provided based on the pooled data across the two arms and by arm.

11.1. HAND ECZEMA (AT BASELINE)

- Involvement (qualitative parameter: “Unilateral”, “Bilateral)
- Involvement (qualitative parameter: “Palmar only”, “Dorsal only”, “Palmar and dorsal)
- Involvement n°1 (qualitative parameter: “Vesicles”, “Cracks”, “Hyperkeratosis”, “Pulpitis”)
- Involvement n°2 (qualitative parameter: “Vesicles”, “Cracks”, “Hyperkeratosis”, “Pulpitis”)
- Involvement n°3 (qualitative parameter: “Vesicles”, “Cracks”, “Hyperkeratosis”, “Pulpitis”)
- Involvement n°4 (qualitative parameter: “Vesicles”, “Cracks”, “Hyperkeratosis”, “Pulpitis”)
- Associated nail disease (qualitative parameter: “Yes”, “No”)

11.2. REMOTE ECZEMA OF THE HANDS (AT BASELINE)

- Eczema away from the hands (qualitative parameter: “Yes”, “No”)
    - If “Yes”, Feet (qualitative parameter: “Yes”, “No”)
    - If “Yes”, Head and neck (qualitative parameter: “Yes”, “No”)
    - If “Yes”, Trunk and/or limbs (excluding folds) (qualitative parameter: “Yes”, “No”)
    - If “Yes”, Folds (qualitative parameter: “Yes”, “No”)

11.3. MODIFIED TOTAL LESION SYMPTOM SCORE (AT BASELINE, V3, V5, V7 AND V9)

- mTLSS achieved (qualitative parameter: “Yes”, “No”)
    - If “No”, why? (qualitative parameter in plain terms)
- mTLSS score (quantitative parameter: from 0 (no symptoms) to 21 (multiple severe symptoms). The result is obtained by adding the score for each of the following items:

Parameter	**Description of severity***
Erythema	0 = Absent 1 = Faint erythema 2 = Prominent redness 3 = Deep intense red color
Scaling	0 = Absent 1 = Slight flaking over limited areas, mostly fine scales 2 = Flaking over widespread area(s), coarser scales 3 = Desquamation covering over 30% of the hand, with coarse thick scales

Lichenification/hyperkeratosis	0 = Absent 1 = Mild thickening with exaggerated skin lines over limited areas 2 = Palpable thickening over widespread area(s) 3 = Prominent thickening over widespread area(s) with exaggeration of normal skin markings
Vesiculation	0 = Absent 1 = Scattered vesicles affecting up to 10% of hand, without erosion 2 = Scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation 3 = High density of vesicles extending over large area(s), or with erosion or excoriation
Oedema	0 = Absent 1 = Dermal swelling over less than 10% of hands 2 = Definite dermal swelling over more than 10% of hand 3 = Dermal swelling with skin induration over widespread area(s)
Fissures	0 = Absent 1 = Cracked skin affecting a small area of the hand 2 = Cracked skin affecting multiple areas of the hand and causing pain 3 = One or more deep fissures and causing bleeding or severe pain
Pruritus/pain	0 = Absent 1 = Occasional, slight discomfort a few times per day 2 = Intermittent, causing discomfort frequently during the day 3 = Persistent or interfering with sleep

*1 = mild; 2 = moderate; 3 = severe

11.4. INVESTIGATOR GLOBAL ASSESSMENT (AT BASELINE, V3, V5, V7 AND V9)

- IGA achieved (qualitative parameter: "Yes", "No")
  - If "No", why? (qualitative parameter in plain terms)
- IGA score (quantitative parameter: from 0 ("Clear") to 4 ("Severe"))

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

- IGA binary score (qualitative parameter: "Clearance or almost clearance", "From mild to severe")

11.5. ECZEMA AREA AND SEVERITY INDEX (AT BASELINE, V3, V5, V7 AND V9)

- EASI achieved (qualitative parameter: "Yes", "No")
    - If "No", why? (qualitative parameter in plain terms)
- EASI score (quantitative parameter: from 0 (no symptoms) to 72 (multiple severe symptoms)). The result is obtained with this scoring table:

Body region	Erythema	Edema/ Papulation	Excoriation	Lichenification	Region score	Multiplier	Score per boy region
Head/neck	(+	+	+	)	×	× 0.1	
Trunk	(+	+	+	)	×	× 0.3	
Upper extremities	(+	+	+	)	×	× 0.2	
Lower extremities	(+	+	+	)	×	× 0.4	
	The final EASI score is the sum of the 4 region scores:						(0 - 72)

    - The severity of each sign (Erythema, Edema/Papulation, Excoriation and Lichenification) is assessed on a scale of 0 to 3 (qualitative parameter: 0="None", 1="Mild", 2="Moderate", 3="Severe")
    - The area of involvement of each body region is assessed on a scale of 0 to 6 (qualitative parameter) based on the following table:

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

11.6. DERMATOLOGY LIFE QUALITY INDEX (AT BASELINE, V3, V5, V7 AND V9)

- DLQI achieved (qualitative parameter: "Yes", "No")
    - If "No", why? (qualitative parameter in plain terms)
- DLQI score (quantitative parameter: from 0 ("Meaning no impact of skin disease on quality of life") to 30 ("Meaning maximum impact on quality of life")). The result is obtained by adding the score for each of the following items:

Item	Quotation
1 - Over the last week, how itchy, sore, painful or stinging has your skin been?	3 = Very much 2 = A lot 1 = A little 0 = Not at all
2 - Over the last week, how embarrassed or self conscious have you been because of your skin?	3 = Very much 2 = A lot 1 = A little 0 = Not at all
3 - Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	3 = Very much 2 = A lot 1 = A little 0 = Not at all or Not relevant
4 - Over the last week, how much has your skin influenced the clothes you wear?	3 = Very much 2 = A lot 1 = A little 0 = Not at all or Not relevant
5 - Over the last week, how much has your skin affected any social or leisure activities?	3 = Very much 2 = A lot 1 = A little 0 = Not at all or Not relevant

6 - Over the last week, how much has your skin made it difficult for you to do any sport?	3 = Very much 2 = A lot 1 = A little 0 = Not at all or Not relevant
7A - Over the last week, has your skin prevented you from working or studying? 7B - If "No", over the last week how much has your skin been a problem at work or studying?	3 = Yes If No, see next 7B 2 = A lot 1 = A little 0 = Not at all
8 - Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	3 = Very much 2 = A lot 1 = A little 0 = Not at all or Not relevant
9 - Over the last week, how much has your skin caused any sexual difficulties?	3 = Very much 2 = A lot 1 = A little 0 = Not at all or Not relevant
10 - 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?	3 = Very much 2 = A lot 1 = A little 0 = Not at all or Not relevant

- DLQI binary score (qualitative parameter: “0 or 1”, “Greater than 1”)

11.7. 5-LEVEL EQ-5D (AT BASELINE, V3, V5, V7 AND V9)

- EQ-5D-5L achieved (qualitative parameter: “Yes”, “No”)
  - If “No”, why? (qualitative parameter in plain terms)
- EQ-5D-5L: 5 domains (qualitative parameter: from “Level 1” to “Level 5”) (2)
  - Presented as 12345 (qualitative parameter: from “Level 1” to “Level 5” for each domain) where 1 represents the score in the first domain (MO: mobility), 2 the score in the second domain (SC: self-care), 3 the score in the third domain (UA: usual activities), 4 the score in the fourth domain (PD: pain/discomfort) and 5 the score in the fifth domain (AD: anxiety/depression).

Item	**Quotation**
Mobility	1 = I have no problems in walking about 2 = I have slight problems in walking about 3 = I have moderate problems in walking about 4 = I have severe problems in walking about 5 = I am unable to walk about
Self-care	1 = I have no problems washing or dressing myself 2 = I have slight problems washing or dressing myself 3 = I have moderate problems washing or dressing myself 4 = I have severe problems washing or dressing myself 5 = I am unable to wash or dress myself
Usual activities	1 = I have no problems doing my usual activities 2 = I have slight problems doing my usual activities 3 = I have moderate problems doing my usual activities 4 = I have severe problems doing my usual activities 5 = I am unable to do my usual activities

Pain / discomfort	1 = I have no pain or discomfort 2 = I have slight pain or discomfort 3 = I have moderate pain or discomfort 4 = I have severe pain or discomfort 5 = I have extreme pain or discomfort
Anxiety / depression	1 = I am not anxious or depressed 2 = I am slightly anxious or depressed 3 = I am moderately anxious or depressed 4 = I am severely anxious or depressed 5 = I am extremely anxious or depressed

- EQ Visual Analogue Scale (VAS): overall health on a scale from 0 to 100 (quantitative parameter)

11.8. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE (AT BASELINE AND V9)

- WPAI achieved (qualitative parameter: "Yes", "No")
  - If "No", why? (qualitative parameter in plain terms)
- WPAI outcomes in impairment percentages (quantitative parameter), with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. The outcomes are calculated from these data:

Questions	**Modality**
Q1 - Are you currently employed (working for pay)?	"No" (skip to question 6) "Yes"
Q2 - During the past seven days, how many hours did you miss from work because of your health problems?	Quantitative parameter
Q3 - During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?	Quantitative parameter
Q4 - During the past seven days, how many hours did you actually work?	Quantitative parameter (if 0, skip to question 6)
Q5 - During the past seven days, how much did health problems affect your productivity while you were working?	Quantitative parameter (from 0 to 10)
Q6 - During the past seven days, how much did health problems affect your ability to do your regular daily activities, other than work at a job?	Quantitative parameter (from 0 to 10)

  - Work time missed in percent (quantitative parameter) calculated as follows: $\frac{Q2}{Q2 + Q4} * 100$
  - Impairment while working due to health in percent (quantitative parameter) calculated as follows: Q5 * 10
  - Overall work impairment due to health in percent (quantitative parameter) calculated as follows: $\frac{Q2}{Q2 + Q4} + [(1 - \frac{Q2}{Q2 + Q4}) * \frac{Q5}{10}] * 100$
  - Activity impairment due to health in percent (quantitative parameter) calculated as follows: Q6 * 10

11.9. PATIENT'S GLOBAL ASSESSMENT OF DISEASE SEVERITY (AT BASELINE, V3, V5, V7 AND V9)

- PaGa achieved (qualitative parameter: "Yes", "No")
    - If "No", why? (qualitative parameter in plain terms)
- PaGa evaluation (qualitative parameter: "Clear", "Almost clear", "Mild", "Moderate", "Severe")
- PaGa binary evaluation (qualitative parameter: "Clearance or almost clearance", "From mild to severe")

11.10. VISUAL ANALOG SCALES OF PRURITUS, PAIN AND SLEEP LOSS (AT BASELINE, V3, V5, V7 AND V9)

- VAS for measuring pruritus achieved (qualitative parameter: "Yes", "No")
    - If "No", why? (qualitative parameter in plain terms)
    - VAS for measuring pruritus in mm (quantitative parameter)
- VAS for measuring pain achieved (qualitative parameter: "Yes", "No")
    - If "No", why? (qualitative parameter in plain terms)
    - VAS for measuring pain in mm (quantitative parameter)
- VAS for measuring sleep loss achieved (qualitative parameter: "Yes", "No")
    - If "No", why? (qualitative parameter in plain terms)
    - VAS for measuring sleep loss in mm (quantitative parameter)

12. STUDY TREATMENT AND CONCOMITANT MEDICATIONS

Unless otherwise specified, analyses will be carried out in a descriptive manner using appropriate statistics as described in Section 6.1. Results will be provided by arm; no result on the pooled data across the two arms will be provided.

12.1. STUDY TREATMENT (PLACEBO, DUPILUMAB)

Analyses will be based on data recorded on eCRF form. Analyses will be carried out on the ITT population.

A study treatment administration is considered as actually received if the associated reported total dose is greater than 0.

12.1.1. Placebo

Analysis of Placebo exposure will include the following:

- Number and percentage of patients who received Placebo, regardless of the amount administered.
- Total number of administrations of Placebo actually received, regardless of the amount administered (quantitative parameter and qualitative parameter: “0”, “1”, “2”, “3”, “4”).
- Received cumulative dose of Placebo in ml (quantitative parameter).
  Received cumulative dose of Placebo (in ml) will be derived as the sum of the reported actual total doses received of Placebo during the different injections.
- Number and percentage of patients with at least one dose reduction/suppression of Placebo, overall and by reason for dose reduction/suppression (that is, “Due to adverse event”, “Due to other than adverse event”; as reported by investigators). Of note, a patient can be counted in more than one reason for dose reduction/suppression since as per protocol nine administrations (including two on the first visit) of Placebo have to be received by patient.
  Tabulated individual data listing will be further provided; listing will include arm as randomly assigned to by the randomization system, arm as actually received, and all study treatment administration data (Placebo and Dupilumab).

12.1.2. Dupilumab

Analysis of Dupilumab exposure will include the following:

- Number and percentage of patients who received Dupilumab, regardless of the amount administered.
- Total number of administrations of Dupilumab actually received, regardless of the amount administered (quantitative parameter and qualitative parameter: “0”, “1”, “2”, “3”, “4”).
- Received cumulative dose of Dupilumab in ml (quantitative parameter).
  Received cumulative dose of Dupilumab (in ml) will be derived as the sum of the reported actual total doses received of Placebo during the different injections.
- Number and percentage of patients with at least one dose reduction/suppression of Dupilumab, overall and by reason for dose reduction/suppression (that is, “Due to adverse event”, “Due to other than adverse event”; as reported by investigators). Of note, a patient can be counted in more than one reason for dose reduction/suppression since as per protocol nine administrations (including two on the first visit) of Dupilumab have to be received by patient.
  Tabulated individual data listing will be further provided; listing will include arm as randomly assigned to by the randomization system, arm as actually received, and all study treatment administration data (Placebo and Dupilumab).

12.2. CONCOMITANT MEDICATIONS

Concomitant medications will include those medications recorded on "Concomitant treatment" eCRF forms and which were received between the first study treatment administration (included) and the last study treatment administration (included).

A medication is defined as being received between the first study treatment administration (included) and the last study treatment administration (included) if:

- Its start date is between the date of the first study treatment administration (included) and the date of the last study treatment administration (included), regardless of its end date.
- Or, its start date is prior to the date of first study treatment administration and its end date is after or equal to the date of first study treatment administration.

In case of completely missing or incomplete medication start date (respectively medication end date), imputed start date (respectively end date), applying imputation rules as defined in Section 6.3.10, will be used to classify in any case medication as concomitant medication or not.

Number and percentage of patients who received concomitant medication(s) will be summarized by arm in the ITT population, and overall.

13. EFFICACY ANALYSIS

13.1. PRIMARY EFFICACY ENDPOINT

13.1.1. Definition and derivation

The primary efficacy endpoint is the percentage change in mTLSS score from baseline to Week 16 (quantitative parameter with one decimal place). It is calculated as follows:

$$\frac{\text{mTLSS score at visit 9} - \text{mTLSS score at visit 1}}{\text{mTLSS score at visit 1}} \times 100$$

Missing data for this criterion will be imputed as described in section 6.3.5 for this analysis.

13.1.2. Primary analysis

Primary analysis of the primary efficacy endpoint will be carried out on the ITT population, using an adjusted approach controlling for those factors on which the randomization is stratified and on the value of the baseline endpoint.
Levels of factors on which the randomization is stratified will be derived from actual data - that is, last investigator eCRF data entry - to compensate for cases where erroneous stratification factor information were given at the time of randomization leading to randomization in a wrong stratum; see Section 8.1 for details of randomization irregularities.

Percentage change in mTLSS score from baseline to week 16 will be compared between Arm A and Arm B using a covariance analysis (ANCOVA) including the group, the stratification factor, the baseline mTLSS score, and the interaction between the treatment arm and the stratification factor as covariables. Initially, a bivariate test will be conducted between the variable to be explained (percentage change of mTLSS) and the treatment arm. The choice of the test will be based on classical criteria such as normality and homoscedasticity. Subsequently, an Analysis of Covariance (ANCOVA) will be performed. If the interaction is not significant ($p \geq 0.05$), it will be excluded from the model. Otherwise, the analysis will be stratified based on the stratification factor.
Finally, we will verify if the conditions for applying ANCOVA are met by examining the distribution of the residuals graphically (normality and homoscedasticity).
In case all assumptions are not met, we will proceed with a linear regression using the same variables as the previous model but employing a more robust approach (10–12) that tolerates heteroscedasticity.
The null hypothesis H_0 is that percentage change in mTLSS score of Arm A is the same as percentage change in mTLSS score of Arm B after adjustment for stratification factor and the baseline score. The alternative hypothesis H_a is that percentage change in mTLSS score of Arm A differs as percentage change in mTLSS score of Arm B after adjustment for stratification factor and the baseline score.
The percentage change based on the treatment arm will be presented as the difference between the percentage change in arm A and the percentage change in arm B after adjustment. It will be presented with its 95% confidence interval (95% CI) constructed using the estimator of the standard variance for ordinary least squares (OLS) regression if the aforementioned hypotheses are met. Otherwise, this confidence interval will be provided using the robust standard errors described by Eicker-Huber-White (10–12) for heteroskedastic models. Finally, the predicted values per treatment group and their difference will be presented with their 95% CI.

These data will be presented in a table such as the one below:

Percentage change in mTLSS	**N**	**β Coefficient**	**β 95% CI**	**p-value**
Treatment arm				
Placebo	n	0		
Dupilumab	n	β_1	(CI_1 ; $CI_{1'}$)	p_1
Randomization stratum				
Presence of a personal history of atopic dermatitis				
No	n	0		
Yes	n	β_2	(CI_2 ; $CI_{2'}$)	p_2
mTLSS score at inclusion	n	β_3	(CI_3 ; $CI_{3'}$)	p_3
Other qualitative parameter of interest				
Modality 1	n	0		
Modality 2	n	β_4	(CI_4 ; $CI_{4'}$)	p_4
Modality 3	n	β_5	(CI_5 ; $CI_{5'}$)	p_5
Other quantitative parameter of interest	n	β_6	(CI_6 ; $CI_{6'}$)	p_6
R - squared			R^2	

Percentage change in mTLSS	**Mean predicted values**	**95% CI**
Treatment arm		
Placebo		(CI ; CI)
Dupilumab		(CI ; CI)
Dupilumab - Placebo		(CI ; CI)

13.1.3. Sensitivity analyses

To evaluate the robustness of the results of the primary analysis of the primary efficacy endpoint, three sensitivity analyses of the primary efficacy endpoint will be performed:

- A similar analysis will be carried out after using the multiple imputation method to deal with missing outcomes, as described in section 6.3.5.
- A similar analysis will be carried out without imputing the missing outcomes. Thus, only participants with complete data concerning outcomes at the visit 9 will be considered in the analysis.
- Finally, a similar analysis will be carried out on the PP population, as described in section 8.2.2.

13.2. SECONDARY EFFICACY ENDPOINTS

Secondary efficacy endpoints will be tested without adjusting for multiplicity. There will be no fixed order of endpoints as this study is not considered a confirmatory phase III study. Secondary analyses will be performed on the ITT population. Levels of factors on which the randomization is stratified will be derived from actual data - that is, last investigator eCRF data entry - to compensate for cases where erroneous stratification factor

information were given at the time of randomization leading to randomization in a wrong stratum; see Section 8.1 for details of randomization irregularities.

13.2.1. Investigator global assessment

Definition and derivation

The efficacy endpoint is based on IGA at the visit 9. The test result is binarised as described in section 11.4. Missing data for this criterion will be imputed as described in section 6.3.6 for these analyses.

Analysis

The proportion of participants with an IGA score of 0 or 1 at the visit 9 will be compared between Arm A and Arm B using a two-sided stratified CMH test controlling for that factor on which the randomization is stratified, based on the general association statistic (13,14), and performed at the type I error significance level of 0.05. The null hypothesis H_0 is that proportion of participants with an IGA score of 0 or 1 of Arm A is the same as proportion of participants with an IGA score of 0 or 1 of Arm B. The alternative hypothesis H_a is that proportion of participants with an IGA score of 0 or 1 of Arm A differs from proportion of participants with an IGA score of 0 or 1 of Arm B.
Let p_{As} be the underlying proportion of responders of Arm A and p_{Bs} be the underlying proportion of responders of Arm B, the null and alternative hypotheses to be tested are as follows:

H_0 (null hypothesis): $p_{As} = p_{Bs}$

H_a (alternative hypothesis): $p_{As} \neq p_{Bs}$

Treatment effect will be presented by the common odds ratio (adjusted odds ratio), then in the case where this odds ratio differs by stratum (if the test of homogeneity of odds ratio is significant with a p-value<0.05), by the odds ratio per stratum. These odds ratio will be given with their CI95% calculated by the exact method.

Point estimate of the proportion of participants with an IGA score of 0 or 1 in each arm, computed using the binomial proportion (maximum likelihood estimate for one-way tables), will also be provided along with the corresponding two-sided 95% exact Clopper-Pearson CI (15). In the case where these results differ by stratum, they will also be provided by randomization stratum.
These data will be presented in a table such as the one below:

	Placebo arm	**95% CI**	**Dupilumab arm**	**95% CI**
IGA at the visit 9				
n/missing	n/na		n/na	
Clearance or almost clearance	n (%)	(CI% ; CI%)	n (%)	(CI% ; CI%)
From mild to severe	n (%)	(CI% ; CI%)	n (%)	(CI% ; CI%)
Common Odds ratio Control arm to Experimental arm			OR (95% CI)	
Two-sided CMH test			p	

13.2.2. Eczema area and severity index

Definition and derivation

The efficacy endpoint is the change in EASI score from baseline to Week 16 (quantitative parameter). It is calculated as follows:

EASI score at visit 9 – EASI score at visit 1

Missing data for this criterion will be imputed as described in section 6.3.6 for these analyses.

The change in EASI score from baseline to Week 16 is also expressed as a percentage. It is calculated as follows:

$$\frac{\text{EASI score at visit 9} - \text{EASI score at visit 1}}{\text{EASI score at visit 1}} \times 100$$

It is then binarised in two ways according to this percentage:

- Percentage of improvement greater than or equal to 75% (qualitative parameter: “Yes”, “No”)
- Percentage of improvement greater than or equal to 90% (qualitative parameter: “Yes”, “No”)

Analysis

This analysis will be performed only on participants with eczema on a part of the body other than the hands, information collected during the baseline disease assessment (Eczema away from the hands (qualitative parameter: “Yes”, “No”)).
Change in EASI score from baseline to last visit will be compared between Arm A and Arm B using an ANCOVA with an analysis similar to the primary endpoint.

The proportion of participants with a percentage of improvement greater than or equal to 75% or 90 % at the visit 9 will be compared between Arm A and Arm B using a two-sided stratified CMH test controlling for that factor on which the randomization is stratified. This analysis will be similar to the previous IGA analysis.

13.2.3. Dermatology life quality index

Definition and derivation

The efficacy endpoint is the change in DLQI score from baseline to Week 16 (quantitative parameter). It is calculated as follows:

DLQI score at visit 9 – DLQI score at visit 1

Missing data for this criterion will be imputed as described in section 6.3.6 for these analyses.

This score is then binarised according to the improvement from baseline, separating participants with an improvement of 4 or more from the others (qualitative parameter), which corresponds to the Minimal Clinically Important Difference (MCID) of the DLQI (16).

The DLQI score at the visit 9 is also used in binary form as described in section 11.6.

Analyses

Change in DLQI score from baseline to the visit 9 will be compared between Arm A and Arm B using an ANCOVA with an analysis similar to the primary endpoint.

The proportion of participants with an improvement of 4 or more at the visit 9 and the participants with a DLQI score of 0 or 1 at the visit 9 will be compared between Arm A and Arm B using a two-sided stratified CMH test controlling for that factor on which the randomization is stratified. These analyses will be similar to the previous IGA analysis.

13.2.4. 5-Level EQ-5D

Definition and derivation

The EQ-5D-5L questionnaire consists of two parts. The first with qualitative data, the second (EQ-VAS) with quantitative data.

On the first part, the 5 components of the EQ5D-5L will be evaluated for each component by comparing the changes between the baseline results and the results at the visit 9 (qualitative parameter). Changes will be categorized in relation to the baseline, as described in the form associated with the questionnaire (2):
- Their health status (for the respective component) is better
- Their health status has worsened
- Their health status remains the same

A variable summarizing this information, proposed by the creators of the questionnaire (2), will then be used: an EQ-5D health state is deemed to be "better" than another if it is better on at least one dimension and is no worse in any other dimension. An EQ-5D health state is deemed to be "worse" than another if it is worse in at least one dimension and is no better in any other dimension. Using that principle to compare a patient's EQ-5D health states between baseline and the visit 9, we get four possibilities (qualitative parameter: "Better", "Worse", "Exactly the same", "Mixed: better on one dimension, worse on another"). This last variable will then be binarized for analysis (qualitative parameter: "Improvement", "No improvement"), separating participants with an improvement ("Better") from those without ("Worse", "Exactly the same", "Mixed: better on one dimension, worse on another").

On the second part, the efficacy endpoint is the change in EQ-VAS from baseline to Week 16 (quantitative parameter). It is calculated as follows:

EQ-VAS at visit 9 – EQ-VAS at visit 1

Missing data for this criterion will be imputed as described in sections 6.3.6 for this analysis.

Analyses

The assessment of the 5 components of the EQ-5D-5L will be conducted for each component by comparing changes between baseline results and results at the visit 9. The comparison of proportions for each category between the two arms will be performed using the appropriate bivariate test according to the expected numbers of each modality, with a type I error significance level of 0.05.
Next, the variable summarizing the information on the evolution of the 5 components of the EQ-5D-5L in two modalities described above will be analyzed. The proportion of participants with an overall improvement in EQ5D components from baseline to the visit 9 will be compared between Arm A and Arm B using a two-sided stratified CMH test controlling for that factor on which the randomization is stratified. This analysis will be similar to the previous IGA analysis.

Change in EQ-VAS from baseline to the visit 9 will be compared between Arm A and Arm B using an ANCOVA with an analysis similar to the primary endpoint.

13.2.5. Work productivity and activity impairment questionnaire

Each WPAI outcome, described in section 11.8 (work time missed, impairment while working due to health, overall work impairment due to health and activity impairment due to health) will be analyzed independently but using the same procedure.

Definition and derivation

The efficacy endpoints are the change in WPAI outcomes from baseline to Week 16 (quantitative parameter in percent). It is calculated as follows:

WPAI outcome at visit 9 – WPAI outcome at visit 1

Missing data for this criterion will be imputed as described in section 6.3.6 for these analyses.

Analyses

Change in WPAI outcomes from baseline to the visit 9 will be compared between Arm A and Arm B using an ANCOVA with an analysis similar to the primary endpoint.

13.2.6. Patient's global assessment of disease severity

Definition and derivation

The efficacy endpoint is based on PaGa score at the visit 9. The test result is binarized as described in section 11.9.
Missing data for this criterion will be imputed as described in section 6.3.8 for these analyses.

Analysis

The proportion of participants with a PaGa score of 0 or 1 at the visit 9 will be compared between Arm A and Arm B using a two-sided stratified CMH test controlling for that factor on which the randomization is stratified. This analysis will be similar to the previous IGA analysis.

13.2.7. VAS for pruritus, pain and sleep loss

Each VAS (pruritus, pain and sleep loss) will be analyzed independently but using the same procedure.

Definition and derivation

The efficacy endpoints are the change in each VAS score from baseline to the visit 9 (quantitative parameter). It is calculated as follows:

VAS score at visit 9 – VAS score at visit 1

Missing data for this criterion will be imputed as described in section 6.3.6 for these analyses.

These score are then binarised according to the improvement from baseline, separating participants with an improvement of 40 or more from the others (qualitative parameter) for VAS scores for pruritus (17), an improvement of 30 or more for VAS score for pain (18), an improvement of 40 or more for VAS score for sleep loss (19),which correspond to the MCID of these VAS.

Analyses

Change in EVA score from baseline to the visit 9 will be compared between Arm A and Arm B using an ANCOVA with an analysis similar to the primary endpoint.

The proportions of participants with VAS scores greater than or equal to will be compared between Arm A and Arm B using a two-sided stratified CMH test controlling for that factor on which the randomization is stratified. This analysis will be similar to the previous IGA analysis.

13.2.8. Laboratory parameters

Each laboratory parameters (haemoglobin, platelets, leukocytes, eosinophils, Immunoglobulin E) will be analyzed independently but using the same procedure.

Definition and derivation

The efficacy endpoints are the change in each level laboratory parameter from baseline (visit 1 for IGEs, inclusion visit for others) to Week 16 (quantitative parameter). It is calculated as follows:

level laboratory parameter at visit 9 – level laboratory parameter at visit 1 or inclusion

Missing data for this criterion will be imputed as described in section 6.3.6 for these analyses.

Analyses

Change in level laboratory parameter from baseline to the visit 9 will be compared between Arm A and Arm B using an ANCOVA with an analysis similar to the primary endpoint.

14. SAFETY ANALYSIS

Analyses will be carried out on the Treated population in the group of treatment corresponding to the treatment actually received, which may differ from the randomization arm in case of error. Analyses will be performed, in a descriptive manner, using appropriate statistics as described in Section 6.1; no statistical test will be performed. Results will be provided by arm; no result on the pooled data across the two arms will be provided.

14.1. PERIODS OF ANALYSIS

The safety analysis runs from the start of the study to the end of the study (Week 20 visit).

14.2. ADVERSE EVENTS

Analysis will be based on data recorded on "Adverse event" eCRF forms.
All expected or unexpected serious adverse events (AE), adverse event of special interest (AESI) (Conjunctivitis), and all unexpected non-serious adverse events, occurring from the date of consent signature, during the study duration, have been collected and documented on an AE form after coding according to the standardized MedDRA medical dictionary.
Thus, the incidences per group of each type of AE according to the Preferred Term (PT) will be presented and organized by System-Organ Class (SOC). If a subject had multiple AEs of the same PT, only one will be counted, so the denominator will be the number of treated subjects and the numerator the number of subjects experiencing at least one AE of that type. The same descriptive table will be presented for serious AEs and for AEs whose causality to the study or treatment is not excluded. Percentages of subjects with at least one AE, at least one serious AE, and at least one AE for which causality to the study or treatment is not excluded will be calculated with exact 95% CI.

A listing of all serious AEs and AESIs will be produced based on the treatment actually received and will contain the following informations:

- Subject and center identifier
- Date of first study treatment administration
- Date of last study treatment administration
- Date and time of the start of the AE
- Date and time of the end of the AE (or mention of the persistence of the adverse event)
- Description of the event ("Reported Term" and "Preferred Term")
- Severity, intensity
- Causality to the trial or trial treatment
- Action on the trial treatment
- Other action and evolution

The following will be presented by arm (Placebo / Dupilumab):

- The incidence of AE and AESIs based on their causality and severity
- The incidence of AE and AESIs leading to the cessation of trial treatment
- AEs and AESIs occurring between the consent signature and the first administration of treatment

In addition to these safety analyses, the percentage of patients reporting injection site reactions will also be presented overall and by group with exact 95% CI together.

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