STATISTICAL TECHNICAL DOCUMENT

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A multi-center, exploratory study to assess dupilumab effect on pruritus neuro-mechanisms in patients with atopic dermatitis

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADCT:	atopic dermatitis control tool
ATC:	anatomic therapeutic class
DLQI:	dermatology life quality index
EASI:	eczema and severity index
EOS:	end of study
HLT:	high level term
IGA:	investigator global assessment
IMP:	investigational medicinal product
MedDRA:	Medical Dictionary for Regulatory Activities
NRS:	numeric rating scale
PCSA:	potentially clinically significant abnormality
POEM:	patient oriented eczema measure
PROMIS:	Patient-Reported Outcomes Measurement Information
PT:	preferred term
Q2W:	every 2 weeks
QoL:	quality of life
SAP:	statistical analysis plan
SAS®:	Statistical Analysis System®
SC:	subcutaneous
SCORAD:	SCORing Atopic Dermatitis
SD:	standard deviation
SEM:	standard error of the mean
SOC:	system organ class
STD:	statistical technical document
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
VAS:	visual analogue scale
WHO-DD:	World Health Organization Drug Dictionary

1 STATISTICAL AND ANALYTICAL PROCEDURES

1.1 INTRODUCTION

The purpose of this document is to provide additional technical details.

A comprehensive and detailed description of strategy and statistical technique used to perform the analysis of data was provided in Section 9 of the protocol (Version 1 dated on 17AUG2020 and Amended version dated on 06JAN2021).

As specified in the protocol, the biomarker analyses will not be part of this document and a specific dedicated statistical analysis plan (SAP) will be produced in addition to this statistical technical document (STD).

Adverse events and medical history terms will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA Version 25.0).

Previous and concomitant medication records will be coded according to the World Health Organization Drug Dictionary (WHO-DD version March 2022).

The reporting of the safety statistical analyses will be programmed according to the recommendations and templates of the BTD-009094 “Summarizing and reporting standard Early Development clinical trial data (except oncology)” Version 4.0 dated 02-Feb-2021. For vital signs parameters, the analyses of abnormalities will be based on the definitions of potentially clinically significant abnormalities (PCSAs) from BTD-009536 “Analysis and reporting of safety data from Clinical Trials through the Clinical Study Report” Version 3.0 dated 24-May-2014 (Appendix 3) and displayed in Section 3.1.

1.2 MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

Following minor changes and clarifications were made to the statistical section of the protocol (amended version dated on 06JAN2021).

1.2.1 Observation period definition

For the AD participants, the overall observation period will be divided into 3 segments as follows:

- The pre-treatment period is defined as the period up to the first investigational medicinal product (IMP) administration.
- The treatment-emergent (TE) period is defined as the period from the IMP administration up to the end of treatment (EOT) visit (included).
- The post-treatment period (ie, the follow-up extension period) is defined as the period from the end of the TE period.

For the healthy participants, the overall observation period will be divided into 2 segments as follows:

- The screening period is defined as the period of 21 days up to the collection of the skin biopsy.
- The observational period is defined as the period of 7 days following collection of the skin biopsy.

1.2.2 Analysis visits

Except for the baselines, only observations from visits and/or timepoints planned in the protocol will be used in descriptive statistics. Usually, all timepoints planned in the protocol should be described.

All the data collected from eDiary (home dosing and patient-reported outcome) were linked to a unique unscheduled or a missing visit in the SDTM database. To perform the analysis by visit, the following visit window algorithm is defined.

VISIT WINDOW ALGORITHM		
Type of data	**Planned visits in the protocol**	**Time interval for analysed visits**
Home dosing		
Dupilumab administration	D29	23 to 36 days after the first IMP administration
	D57	51 to 64 days after the first IMP administration
	D71	65 to 78 days after the first IMP administration
	D85	79 to 92 days after the first IMP administration
	D99	93 to 106 days after the first IMP administration
Patient-Reported Outcomes		
Peak pruritus NRS	D1	Less than 28 days before the first IMP administration
	From D2 to D28	x days after the first IMP administration for each Dx
	D36	29 to 39 days after the first IMP administration
	D43	40 to 46 days after the first IMP administration
	D50	47 to 53 days after the first IMP administration
	D57	54 to 60 days after the first IMP administration
	D64	61 to 67 days after the first IMP administration
	D71	68 to 74 days after the first IMP administration
	D78	75 to 81 days after the first IMP administration
	D85	82 to 88 days after the first IMP administration
	D92	89 to 95 days after the first IMP administration
	D99	96 to 102 days after the first IMP administration

VISIT WINDOW ALGORITHM		
Type of data	**Planned visits in the protocol**	**Time interval for analysed visits**
	D106	103 to 109 days after the first IMP administration
	D113	110 to 116 days after the first IMP administration
	D120	117 to 123 days after the first IMP administration
	D127	124 to 130 days after the first IMP administration
	D134	131 to 137 days after the first IMP administration
	D141	138 to 197 days after the first IMP administration
Sleep quality NRS Skin pain NRS Skin Sensitivity NRS Skin Burning NRS	D1	Less than 28 days before the first IMP administration
	D15	2 to 29 days after the first IMP administration
	D43	30 to 57 days after the first IMP administration
	D71	58 to 85 days after the first IMP administration
	D99	86 to 106 days after the first IMP administration
	D113	107 to 127 days after the first IMP administration
	D141	128 to 197 days after the first IMP administration
POEM DLQI PROMIS-itch	D1	Less than 28 days before the first IMP administration
	D43	2 to 57 days after the first IMP administration
	D71	58 to 85 days after the first IMP administration
	D99	86 to 106 days after the first IMP administration
	D113	107 to 127 days after the first IMP administration
	D141	128 to 197 days after the first IMP administration

If more than one record occurs within the same visit window where only one assessment is expected, then the following rule will be applied: for D1, the last non-missing result prior to study drug administration will be used; for post-treatment assessments the closest non-missing result to the scheduled visit will be used. Then, for post-treatment assessments, if more than one record remain analyzable (ie, two records or more the same day), the first one will be used.

1.2.3 Participant demographic characteristics, medical history, and diagnoses

1.2.3.1 Other baseline characteristics

As there are not any other baseline characteristics, the planned listing will not be produced.

1.2.3.2 Medical/surgical history

Medical/surgical histories will be summarized by system organ class (SOC), high level term (HLT) and preferred term (PT), and listed.

1.2.4 Compliance

As the exact dose is not recorded in the database for the home dosing, the above-planned and under-planned dosing percentages will not be analyzed.

1.2.5 Prior/Concomitant medication/therapy

Concomitant medications will be summarized by anatomic category (first digit of the anatomic therapeutic class (ATC)) and therapeutic category (first three digits of the ATC). All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, participants may be counted several times for the same medication.

A specific listing of rescue medications will also be performed. The rescue medications will be identified with “RESCUE THERAPY” as reason for treatment. The following information will be added in the listing: demographic data, dose regimen, reason for treatment...

1.2.6 Efficacy analyses

No imputation will be performed for the following efficacy analyses.

1.2.6.1 Primary endpoints

The two primary endpoints (intraepidermal nerve fiber density and branching by PGP9.5 antibody staining in lesional skin) was planned to be analyzed as quantitative endpoints. But the branching is a semi-quantitative endpoint with 4 modalities: “only linear”, “mainly linear”, “mainly branched” and “only branched” fibers. The statistical method will be updated as follows:

- The number and percentage of participants for each modality will be described by timepoints, by skin type (Lesional pruritic skin, Post-lesional healed skin non-pruritic non-lesional, Lesional non-pruritic skin and Non-lesional skin) and by treatment group based on the mITT and ITT population. Only the evaluable participants will be taken into account in the calculation of the percentages.
- The listing of individual data will be performed, including the following information: demographic data, location, laterality and directionality...
- No plots will be performed.

To analyze the change from baseline on Week 17 for intraepidermal nerve fiber density by PGP9.5 antibody staining in lesional skin, the summary plots for AD participants based on the mITT population (and on the ITT population) will be graphs of mean +/- standard error of the mean (SEM) for raw data, absolute and percent change from baseline at baseline (ie, 0) and Week 17.

1.2.6.2 Secondary endpoints

To analyze the changes from baseline on Weeks 3 and 21 for intraepidermal nerve fiber density and branching by PGP9.5 antibody staining in lesional skin, the summary plots for AD participants based on the mITT population (and on the ITT population, if applicable) will be graphs of mean +/- SEM for raw data, absolute and percent change from baseline at baseline (ie, 0), Week 3 and Week 21.

To analyze the changes from baseline on Weeks 3 and 21 for intraepidermal nerve fiber density and branching by PGP9.5 antibody staining in lesional skin and changes from baseline over time and at Weeks 17 and 21 for the outcomes of the assessments/questionnaires (peak pruritus assessed by numeric rating scale (NRS), eczema and severity index (EASI), scoring atopic dermatitis (SCORAD), patient-reported outcomes measurement information (PROMIS-itch), patient oriented eczema measure (POEM), dermatology life quality index (DLQI), atopic dermatitis control tool (ADCT) and sleep quality/skin pain/skin sensitivity/skin burning NRS), the individual profiles over time will be spaghetti plots on raw data with all the AD participants on the same graph and the AD group mean.

To analyze the changes from baseline over time and at Weeks 17 and 21 for the outcomes of the assessments/questionnaires, the following variables will be analyzed:

- Peak pruritus assessed by numeric rating scale (NRS): scale of the worst itch (from 0 (“no itch”) to 10 (“Worst itch imaginable”)).
- Eczema and severity index (EASI): composite index ranging from 0 to 72 calculated as follows. The intermediate and total EASI scores will be derived, however, only the total EASI score will be analyzed.
  - Severity scores: for each region (Head and neck, Trunk, Upper limbs and Lower limbs), the severity score will be derived as follows, ranging from 0 to 12:

    $$\text{Severity score}_{R} = \text{Intensity score}_{\text{Erythema, R}} + \text{Intensity score}_{\text{Edema/Papulation, R}} + \text{Intensity score}_{\text{Excoriation, R}} + \text{Intensity score}_{\text{Lichenification, R}},$$

    where R = region.
  - Region scores: for each region, the region score will be derived as follows:

    $$\text{Region score}_{R} = \text{Severity score}_{R} * \text{Area score}_{R} * \text{Multiplier}$$

    where R = region, Multiplier = 0.1 for Head and Neck region, 0.3 for Trunk, 0.2 for Upper Limbs, 0.4 for Lower Limbs.
  - Total EASI score will be derived as the sum of the 4 region scores.
- Scoring Atopic Dermatitis (SCORAD): intermediate SCORAD scores (A/B/C) and total SCORAD score calculated as follows. The intermediate and total SCORAD scores will be derived, however, only the total SCORAD score will be analyzed.

  $$\text{SCORAD score} = A/5 + 7*B/2 + C, \text{ where}$$

  A is the sum of each extent of AD (Left and Right Lower Limbs, Left and Right Upper Limbs, Anterior Trunk, Head and Neck, Genitalia and Posterior Trunk) in %;

B is the sum of severity scales of each symptom of AD (Dryness, Edema/Papulation, Erythema, Excoriation, Lichenification and Oozing/Crust) (scale from 0 to 3);

C is the sum of visual analogue scale (VAS) of itch and sleeplessness (VAS from 0 to 10).

- Investigator global assessment (IGA): 5-point scale to rate the severity of AD globally ranging from 0 (clear) to 4 (severe).
- Patient-Reported Outcomes Measurement Information (PROMIS-itch):
  - Itch-Severity: scores of each of 7 quantitative items and total score.
  - Itch-Activity and Clothing: scores of each item.
  - Itch-Mood and Sleep: scores of each item.
  - Itch-Interference: scores of each item.
  - Itch-Scratching Behavior: scores of each item.
  - Itch-Quality and Itch-Triggers: not applicable (Yes-No answers).
- Patient Oriented Eczema Measure (POEM): total score (sum of the 7 items) ranging from 0 to 28. A high score indicates a high severity.
- Dermatology Life Quality Index (DLQI): total score (sum of the 10 items) ranging from 0 to 30. A high score indicates a poor quality of life (QoL).
- Atopic Dermatitis Control Tool (ADCT): total score (sum of the 6 items) ranging from 0 to 24. A high score indicates a low AD control.
- Sleep Quality NRS: scale of the sleep quality [from 0 (“Worst possible sleep”) to 10 (“Worst pain possible”)].
- Skin Pain NRS: scale of the skin pain [from 0 (“No pain”) to 10 (“Worst pain possible”)].
- Skin Sensitivity NRS: scale of the skin sensitivity [from 0 (“Normal”)) to 10 (“Extremely sensitive”)].
- Skin Burning NRS: scale of the skin burning [from 0 (“Not at all”)) to 10 (“Very much”)].

To analyse the proportion of AD participants reaching pruritus NRS ≥4 point improvement from baseline at Weeks 3, 7, 11, 15, 17 and 21 for each NRS scale (Sleep Quality, Skin Pain, Skin Sensitivity and Skin Burning), a participant will be considered to reach a pruritus NRS ≥4 point improvement at a given time point if he presents a change from baseline ≥4 at the timepoint.

1.2.6.3 Exploratory endpoints

Not applicable (biomarker analyses).

1.2.7 Safety analyses

1.2.7.1 Physical examination

As the clinically significant abnormality in physical examination is not recorded in the database, only the number and percentage of participants with at least one post-baseline abnormality in physical examination will be summarized and listed by treatment group.

1.3 DATA HANDLING CONVENTIONS

This section describes the rules and conventions used in the presentation and analysis of data.

In the statistical appendices and in-text tables, the following study group label will be used:

- Healthy Participant.
- Dupilumab *(identified as "patient group" in the protocol).*

All individual data for all included participants will be presented in data listings, sorted by study group and participant number.

In listings, no date of assessments/events/medications will be presented but only the relative day. It will be calculated as follows:

- For AD participants: relative day = date of assessments/events/medications – date of first IMP administration +1.
- For healthy participants: relative day = date of assessments/events/medications – date of D1 visit +1.

For parameters with evaluations before administration and in cases of rechecked value(s) for one participant, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values. After baseline, only observations planned in the protocol will be used in descriptive statistics.

If not otherwise stated in the statistical section of the protocol:

- Missing data other than protocol-planned baseline values will not be replaced.
- Descriptive statistics for quantitative parameters will be provided using number of observations (N), mean, standard deviation (SD), SEM, median, minimum and maximum. The 95% confidence interval will be added for efficacy analyses.
- Descriptive statistics for qualitative parameters will be provided using frequencies (N) and percent (%).

Handling missing data for adverse events

In case of missing or inconsistent information, an AE will be counted as a treatment-emergent AE (TEAE), unless it can clearly be ruled out that it is not a treatment-emergent adverse event (eg, by partial dates or other information).

If the start date (or time) of an AE is incomplete or missing, it will be counted as TEAE except if an incomplete date (or time) or comment indicates that it is a pre- or post-treatment event.

If the relationship to study intervention is missing for an AE, this AE will be assessed as unrelated if it started before administration of study medication; in all other cases it will be assumed to be related.

If the severity is missing for one of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

2 SOFTWARE DOCUMENTATION

The analysis of clinical data will be performed under the responsibility of Sanofi Biostatistics Department, using SAS® (SAS Institute, NC USA).

3 APPENDICES

3.1 POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES CRITERIA

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for Phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.