16.1.9 Documentation of statistical methods

16.1.9.1 Final statistical analysis plan (and amendments)

This section contains the following document:

Statistical Analysis Plan version 2.0, dated 24 Feb 2022

Addendum to Statistical Analysis Plan for LPS16677 version 1.0, dated 09 Oct 2023

NCT04502862

Sanofi-Aventis Recherche & Développement (SARD)

Dupilumab (SAR231893) - LPS16677

A Phase 4, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of the effect of dupilumab on sleep disturbance in patients with uncontrolled persistent asthma

24FEB2022

Statistical Analysis Plan

Final Version 2.0

Prepared by: [redacted]

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ACQ	Asthma Control Questionnaire
ADSD	Asthma Daytime Symptom Diary
AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
ALT	Alanine Transaminase
ANSD	Asthma Nighttime Symptom Diary
[redacted]	[redacted]
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BCP	Business Continuity Plan
BD	Bronchodilator
CI	Confidence Interval
CLINRO	Clinician-Reported Outcome
CP	Conditional Power
CRSwNP	Chronic rhinosinusitis with nasal polyps
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ERS	European Respiratory Society
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume
FVC	Forced Vital Capacity
HLT	High Level Term
HLGT	High Level Group Term
HR	Heart Rate
IA	Interim Analysis
IcEv	Intercurrent Event

ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LABA	Long-Acting Beta2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
LLT	Lowest Level Term
LS	Least Squares
LTRA	Leukotriene Receptor Antagonist
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NIMP	Non-Investigational Medicinal Product
NRS	Numerical Rating Scale
[redacted]	[redacted]
PCSA	Potentially Clinically Significant Abnormalities
[redacted]	[redacted]
PRO	Participant-Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
[redacted]	[redacted]
PT	Preferred Term
Q1	First Quartile
Q2W	Every 2 Weeks
Q3	Third Quartile
ROW	Rest of World
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCS	Systemic Corticosteroids
SD	Standard Deviation
[redacted]	[redacted]
SoA	Schedule of Activities
SOC	System Organ Class
[redacted]	[redacted]
SMQ	Standardized MedDRA Query
SV	Screening Visit
TEAE	Treatment-Emergent Adverse Events
TLFs	Tables, Listings, Figures
[redacted]	[redacted]
ULN	Upper Limit of Normal
WASO	Wake After Sleep Onset
[redacted]	[redacted]
WHO-DD	World Health Organization-Drug Dictionary

1. Introduction

This document provides the detailed statistical methodology for the analysis of data from the Sanofi-Aventis Recherche & Développement (SARD) study LPS16677. The table, listing and figure shells supporting the Statistical Analysis Plan (SAP) can be found in a separate SAP shell document.

The analyses described herein are based on the Amended Protocol 1, Version 1.0, dated on 17th September 2020. Any changes or revisions to the planned analysis described in this document will be made prior to database lock.

2. Study Objectives, Endpoints and Estimands

The study objectives and corresponding endpoints are shown in the Table 2-1;

Table 2-1 Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the effect of dupilumab on sleep in participants with moderate-to-severe asthma	• Change from baseline to Week 12 in sleep disturbance score using the Asthma Sleep Disturbance Questionnaire
Secondary	
• To evaluate the effect of dupilumab on additional participant reported sleep outcome	• Change from baseline to Week 12 on the number of nocturnal awakenings (Sleep Diary) • Change from baseline to Week 12 in Patient-Reported Outcomes Measurement Information System (PROMIS) sleep-related impairment Short Form 8a scale • Change from baseline to Week 12 in sleep quality (Sleep Diary) • Change from baseline to Week 12 in restorative sleep (Sleep Diary) • Change from baseline to Week 12 in wake after sleep onset (WASO) (Sleep Diary)
• To evaluate the effect of dupilumab on objective sleep assessment	• Change from baseline to Week 12 in WASO based on actigraphy data
• To evaluate the effect of dupilumab on asthma symptoms	• Change from baseline to Week 12 in Asthma Daytime Symptom Diary (ADSD) and Asthma Nighttime Symptom Diary (ANSD)
• To evaluate the effect of dupilumab on lung function	• Change from baseline to Week 12 in prebronchodilator forced expiratory volume (pre-BD FEV_1)
• To evaluate the safety of dupilumab	• Incidences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) including clinically significant changes in vital signs

- Incidences of adverse events of special interest (AESI)

[redacted]

Table 2-2 Summary of primary estimands for main objectives

Endpoint Category (estimand)	**Estimands**			
	Endpoint[a]	**Population**	**Intercurrent event handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To assess the effect of dupilumab on sleep				
Primary endpoint	Change from baseline to Week 12 in sleep disturbance score using the Asthma Sleep Disturbance Questionnaire	ITTp	• Discontinuation of study intervention due to Covid-19 pandemic[b] (IcEv1), off-study intervention data will be set as missing (hypothetical strategy). • Discontinuation of study intervention not due to Covid-19 pandemic (IcEv2), all data collected following schedule after the study intervention discontinuation will be used in the analysis (treatment policy strategy).	A mixed effect model for repeated measures (MMRM) under the missing at random (MAR) assumption will be used. The MMRM will include study intervention, age, BMI, stratum (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, rest of world [ROW] with high ICS dose and ROW with medium ICS dose), inclusion in [redacted] visit, study intervention-by-visit interaction, baseline ACQ-5, baseline sleep disturbance score and baseline sleep disturbance score-by-visit interaction all as covariates. Stratification factors, study intervention and visit will be included as categorical parameters.

Endpoint Category (estimand)	Estimands			
	Endpoint[a]	**Population**	**Intercurrent event handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary objective: To evaluate the effect of dupilumab on additional participant reported sleep outcome.				
Secondary endpoint	Change from baseline to Week 12 in number of nocturnal awakenings (Sleep Diary)	ITT	Same as the primary endpoint	The same MMRM as for the primary estimand (primary objective), with the baseline values corresponding to the outcome variables.

a Additional endpoints (secondary or tertiary) that are not included in this table will be handled with a similar analysis according to the endpoint type (i.e., continuous, binary, time-to-event) but without formal testing (i.e., nominal p-value provided for descriptive purpose only). The other secondary/tertiary endpoints are listed in Section 8.2.

b The Covid-19 pandemic is unexpected and will eventually be over. The objective of the present study is to evaluate the treatment effect in absence of the pandemic and therefore the data collected after study intervention discontinuation due to pandemic will be set to missing.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase IV, 1:1 randomized, parallel, multicenter study, with a 12-week double-blind placebo-controlled treatment period to assess the effect of dupilumab in improving sleep outcomes, asthma control, and health related quality of life, and in reducing daytime and nighttime asthma symptoms.

Approximately 260 participants will be randomly assigned to study intervention in a 1:1 Dupilumab to placebo ratio to achieve 234 evaluable participants for an estimated total of 117 evaluable participants per study intervention group.

The study will comprise of:

- Screening Period 1 (Day -35 to -12 from signed informed consent): Participants will be evaluated according to inclusion and exclusion criteria
- Screening Period 2 (Day -11 to -1; pre-baseline assessments): eligible participants will complete the assessments specified in the schedule of activities (SoA).
  If preferred by the participant and the investigator for logistical reasons, screening visit 1 and screening visit 2 can be merged into a single on-site visit which will have to be done on Day -11 at the latest
- Baseline (Day 1): Participants who remain eligible will be randomized
- Randomized double-blind placebo-controlled treatment period (12 weeks from baseline): Participants will be randomized to receive either Dupilumab or placebo
- Post-treatment follow-up period: up to 12 weeks after last dose of IMP or until the participant switches to commercialized dupilumab (or other biologic product), whichever comes first.

Study duration for each participant will be approximately 16 weeks and up to 29 weeks. A participant is considered to have completed the study if he/she has completed all phases of the study including the post treatment follow-up visit.

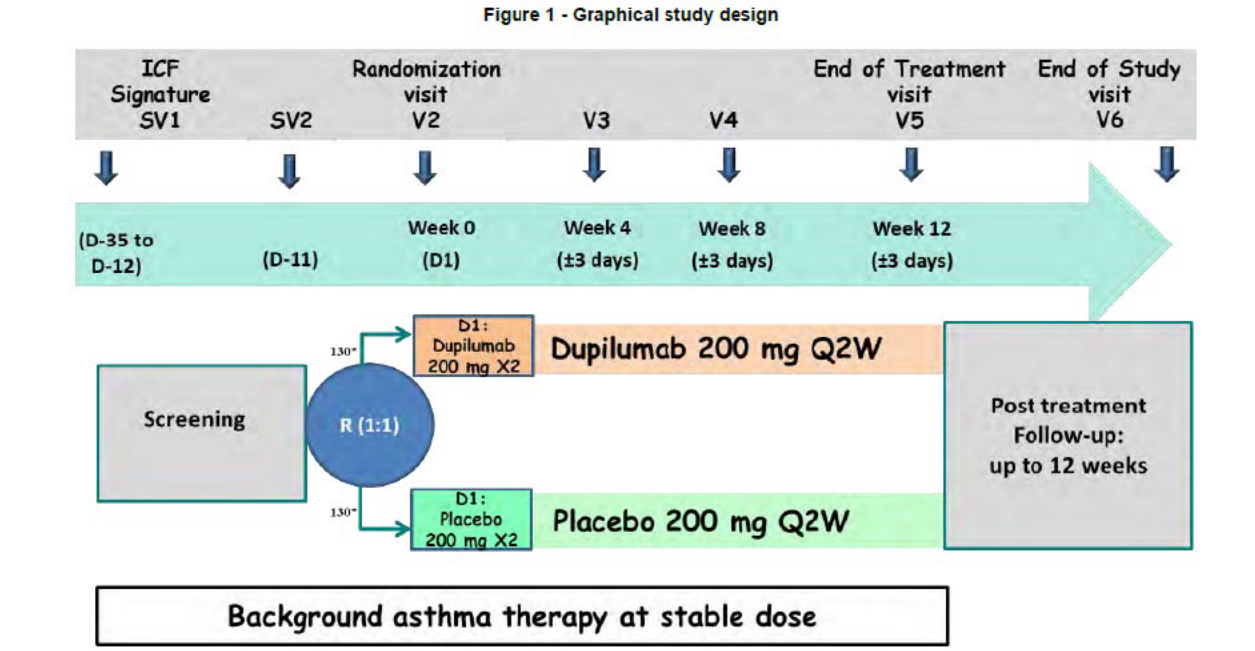
The end of the study is defined as the date of the last visit of the last participant in the study.

The study analysis will be conducted in two steps. A primary database lock will be performed when all randomized participants will have completed the Week 12 visit or will have discontinued the study. The database will be updated at the end of the study for all participants to include the post-treatment follow-up information and updates for the events previously ongoing at the time of the primary lock. The CSR will include analyses from both the primary database lock and the final database lock.

Analysis methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable.

The Sleep Disturbance Questionnaire (assessment of primary endpoint) has been updated in the Amended Protocol 01. The participants already enrolled in the study who completed the initial version of the questionnaire will be excluded from the primary analysis to mitigate the risk of potential different responses before and after the protocol amendment.

Figure 3-1 Study Plan



[redacted]

3.2. Study Endpoints

The study objectives and corresponding endpoints are shown in the Table 2-1 Objectives and endpoints.

3.3. Study Interventions

The dose selected in this study has been evaluated in Dupilumab pivotal trials and approved by regulatory authorities, demonstrating a positive benefit/risk balance.

Participants will receive either;

- Dupilumab 400 mg (2 x 200 mg Dupilumab subcutaneous injections) on Day 1 (loading dose), followed by 1 Dupilumab injection of 200 mg every two weeks (Q2W) until Week 12.
- Matching placebo for Dupilumab (2 x 200 mg placebo subcutaneous injections) on Day 1 (loading dose), then 1 placebo injection Q2W until Week 12.

A home dosing diary will be provided to collect information related to at home injections.

Non-investigational medical products (NIMP)

Participants should be treated with medium to high dose of inhaled corticosteroids (ICS) and a second controller (i.e., LABA, LTRA). A third controller is allowed but not mandatory. The dose regimen should be stable for ≥1 month before SV1, during the Screening and treatment Periods. Short-acting β 2 agonists may be used as rescue medication during the study if needed. In case of asthma exacerbations, the systemic corticosteroids are allowed as rescue medication as well. An asthma background therapy diary will be provided to collect information related to NIMP use.

3.4. Dose Adjustment/Modifications

Not applicable.

4. General Statistical Considerations

4.1. Sample Size

The sample size was chosen to enable an adequate characterization of the efficacy between dupilumab 200 mg Q2W and placebo with regards to the primary endpoint, change from baseline in sleep disturbance score at Week 12 in participants with moderate to severe asthma.

The sample size calculation was based on the subset of adult participants who had more than 1 weekly average nocturnal awakening at baseline, baseline ACQ-5 ≥2.5, baseline blood eosinophis ≥150 cells / μ L and baseline FeNO ≥25 ppb in the previous [redacted] evaluating efficacy of dupilumab for participants with moderate to severe asthma.

The observed treatment difference on mean sleep disturbance score of the dupilumab group with 200 mg Q2W dosing in [redacted] versus placebo at Week 12 was [redacted]. A conservative estimate was used that assumes the treatment difference to be [redacted] at Week 12. Assuming normal distribution of the change in sleep disturbance score, a common standard deviation (SD) of [redacted], which came from the observed data in [redacted], with 117 participants per group, the study would have 90% power to detect a mean treatment difference of [redacted] using a two-sided test with alpha=0.05 for change from baseline in sleep disturbance score at Week 12 in the dupilumab 200 mg Q2W group versus placebo.

Assuming a 10% dropout rate, approximately 260 participants will be randomly assigned to study intervention to achieve 234 evaluable participants for an estimated total of 117 evaluable participants per intervention group. In order to mitigate the risk of potential different responses based on the Sleep Disturbance Questionnaire before and after amendment 01, the primary analysis of change from baseline in sleep disturbance score will exclude the participants who use the original questionnaire at baseline. The number of participants randomized up to the implementation of this protocol amendment is limited (ie, ≤ 10); therefore, the study power can be preserved at ≥89% and therefore no participant replacement is planned.

A large variability of placebo effects was observed between 200 mg and 300 mg placebo arms from [redacted] The current treatment effect assumption was based on 200 mg placebo and 200 mg dupilumab arm. The impact of large variability of placebo effects on study power will be mitigated by conducting an interim analysis (IA) (see Section 12), and the final sample size will be determined by sample size re-estimation procedure based on the observed treatment effect at the time of the IA. The sample size may be increased up to a cap of 520 total randomized participants (260 each arm).

4.2. Randomization, Stratification, and Blinding

Randomization will be stratified according to 5 strata: one stratum for all participants included in the [redacted] (regardless of dose level of ICS, regardless of region) and 4 strata for participants not included in [redacted], according to region and ICS dose (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, rest of world [ROW] with high ICS dose, and ROW with medium ICS dose). In total, no less than 40% participants need to be in "high ICS" strata, and no more than 25% participants need to be in "Eastern Europe" strata.

A participant who has been allocated to a randomized intervention regardless whether the intervention kit was used or not will be considered a randomized participant. A participant cannot be randomized more than once in the study.

4.3. Analysis Sets

Participants exposed to IMP before or without being randomized will not be considered randomized, will not be included in any analysis set and will be reported in listings under a study intervention group named "not randomized but treated". However, if these participants experienced any safety event, they would be documented separately in the clinical study report.

Participants randomized but not treated will be included in all efficacy analyses. These participants will be analyzed for efficacy analyses according to the study intervention group to which they are allocated by the interactive voice response system (IVRS).

4.3.1. Screened Analysis Set

The Screened analysis set includes all participants who sign the informed consent form (ICF).

4.3.2. Intent-to-Treat (ITT) Analysis Set

The ITT analysis set consists of all randomized participants (i.e., participants with a study intervention kit number allocated and recorded in the IVRS database, regardless of whether the study intervention kit was used or not). Participants in the ITT analysis set will be analyzed according to the study intervention group allocated by randomization. This analysis population will be applied to all efficacy analyses except that of the primary endpoint.

4.3.3. Intent-to-Treat for primary endpoint (ITTp) Analysis Set

The ITTp analysis set consists of all ITT participants excluding those who used the original version of sleep disturbance questionnaire at baseline and/or post-baseline. This analysis population will only be applied to primary endpoint analysis.

[redacted]

4.3.5. Safety Analysis Set

The Safety analysis set includes all randomized participants who received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. Randomized participants for whom it is unclear whether the study medication was taken will be included in the safety analysis set as randomized. For participants receiving more than one IMP during the study (i.e., placebo and dupilumab), the actual study intervention group for as treated analysis will be the dupilumab group.

4.4. Reporting Conventions

Statistical analysis will be performed using SAS® Version 9.4 or higher.

Standardized and validated SAS macros from PPD will be used to set-up table, listing, figure (TLF) formats (headers/footers and tabulation format) and tabulate the summaries. All tables and listings will be independently validated using double programming; all figures will be independently validated manually.

4.4.1. Study Intervention labels

The following study intervention labels will be used in the Tables, Figures and Listings:

Table 4-1 Study Intervention labels

Study Intervention order	Study Intervention group	Study Intervention Label
1	Placebo	Placebo
2	Dupilumab 200 mg q2w	Dupilumab 200 mg q2w
3	Total	Total

4.4.2. Visit naming Conventions

The electronic Case Report Form (eCRF) visit label will be used to classify the assessments. Where applicable, visit name will be formatted as "Week X" in summaries.

4.4.3. Visit Windows

The visit windows as defined in Section 15.5 will be applied to all endpoints.

4.4.4. Unscheduled Visits

Unscheduled visit measurements will be used in the analysis on efficacy variables and will be included in the by-visit summaries for the safety variables if they are re-allocated to scheduled visits according to the visit window definitions in section 15.5.

4.4.5. Display of Data Summary and Analysis

Continuous variables will be summarized using descriptive statistics, including the following: sample size (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum for each study intervention group.

All mean, Q1, Q3 and median values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value. Minimum and maximum will be formatted to the same number of decimal places as the measured value.

95% confidence intervals (CIs) will be two-sided and displayed to the same level of precision as the statistic they relate to. If an estimate or a CI is not estimable, it will be presented as 'NE'. If neither an estimate, nor its CI are estimable, it will be presented as simply 'NE', not displaying 'NE' twice.

The p-values will be two-sided and will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as '<0.001'.

Categorical and ordinal data will be summarized using the counts and percentages. When count data are presented, the percent will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted 'Missing" will be included in count tabulations for demographics, baseline characteristics and compliance to account for missing values. No percentages will be displayed on the 'Missing' rows and the percentages on the other rows will be based on the number of non-missing observations. Unless otherwise specified, the denominator for all other percentages will be the number of participants in that study intervention within the specific analysis set of interest. All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x), where the percentage is in the parentheses. When the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0), unless otherwise specified.

All listings will be sorted for presentation in order of assigned study intervention arm, study center number, participant number and date of procedure or event.

4.4.6. Baseline, study day and duration derivations

For assessments to be completed daily during the week prior to baseline visit (i.e., asthma sleep disturbance questionnaire, actigraphy parameters, sleep diary, ADSD and ANSD), the baseline value will be calculated by averaging the data collected/recorded from Day -6 to Day 1 (for ADSD: from Day -7 to Day -1). For actigraphy parameters, assessments performed at the same date as Day 1 will be taken into account for baseline calculation only if the end time of assessment is before 12 pm, reflecting the last night before the visit.

If less than 4 measurements are available between Day -6 and Day 1 (for ADSD: between Day -7 and Day -1), the most recent 4 measurements will be used for the calculation; if finally, less than 4 measurements are available, it will be considered as missing.

For all the other parameters, the baseline value is generally defined as the last available valid (non-missing) value up to and including the day of first dose of IMP. For participants randomized but not treated, the baseline value is defined as the last available value up to and including the day of randomization.

If multiple valid values of a variable (efficacy or safety) exist within a same day (and the recorded times of measurement do not enable to identify which of them is the last assessment), the value measured during the scheduled visit will be used as Baseline in the analysis. If none of those values were assessed during a scheduled visit, then all these measurements will be used for the analysis and the average will be calculated to derive the baseline value.

Baseline safety and efficacy results are presented in the safety and efficacy analyses.

The reference day (denoted as Day 1) for the calculation of extent of exposure and study day for AE listings will be the day of the first administration of IMP:

- Extent of exposure (see Section 7.2.1)
- Study day for AE listing: AE onset date – first administration date of IMP + 1

The reference day (denoted as Day 1) for the calculation of study day of efficacy assessments will also be the day of the first administration of IMP (except for participants randomized but not exposed).

- For visit prior to the first administration of IMP, study day = assessment date – the first administration of IMP.
- For visit at or after the first administration of IMP, study day = assessment date – the first administration of IMP + 1.

Note: For participants randomized but not treated, the reference day will be the randomization date.

Intervals that are listed and/or tabulated in weeks will be transformed from days to weeks by using (without rounding) the following conversion formula:

WEEKS = DAYS /7

Intervals that are listed and/or tabulated in months will be transformed from days to months by using (without rounding) the following conversion formula:

MONTHS = DAYS /30.4375

The last on-treatment value of safety parameters is the final measurement assessed during the treatment-emergent adverse event period regardless of the introduction of rescue therapy and including measurements at unscheduled visits.

4.4.7. Change from baseline

Change from baseline is defined as: Change from baseline = Value at specific time point – Baseline value.

4.5. Intercurrent Event Types

Table 4-2 specifies the types of Intercurrent events (IcEvs), and associated labels, used to define the estimands.

Table 4-2 Intercurrent Event Types

Label	Intercurrent Event Type
IcEv1 (discontinuation of study intervention due to Covid-19)	Premature study intervention discontinuation due to Covid-19 pandemic before Week 12
IcEv2 (discontinuation of study intervention not due to Covid-19)	Premature study intervention discontinuation not due to Covid-19 pandemic before Week 12

5. Participant Disposition

5.1. Disposition

The participant disposition will be summarized for the ITT analysis set by study intervention group and overall using number and percentage. This section describes participant disposition for both participant study status and the participant analysis sets.

For participant study status, the number and percentage of participants in the following categories will be presented:

- Screened participants
- Screen failure participants
- Participants treated without being randomized
- Randomized participants
- Randomized but not treated participants
- Randomized and treated participants
- Participants who have completed the treatment period
- Participants who did not complete the treatment period and the main reason for study intervention discontinuation. Relationship with COVID-19 will be reported for “Adverse Event” and “Other” reasons.
- Participants who completed the study
- Participants who did not complete the study and the main reason for study discontinuation. Relationship with COVID-19 will be reported for “Other” reasons
- Participants who discontinued the study before Week 12
- Participants who discontinued the study after Week 12 (i.e., during post-treatment follow-up period)
- Participants who had rescue medications:
    - Participants who have completed the treatment period and had rescue medications
    - Participants who did not complete the treatment period and had rescue medications

- Final Study Status

For screened, screen failure, and participants treated without being randomized, percentages will be calculated using the number of screened participants as the denominator for overall only. All other categories of participants will be presented by randomized study intervention group and for overall whilst the percentages will be calculated using the number of randomized participants within each study intervention group and overall, as denominator. Reasons for study intervention and study discontinuation will be supplied in the disposition table showing number and percentage by study intervention group.

Participants with permanent study intervention and study discontinuation (early withdrawals) will be identified and described in separate listings.

A summary of all the analysis sets for safety and efficacy (ITT, ITTp, and [redacted] will be summarized for the ITT analysis set by study intervention group and overall using number and percentage.

Additionally, trial impact (disruption) due to COVID-19 pandemic will be presented on ITT population and will be considered for a participant if at least one of those events occur during the study:

- Permanent end of study intervention due to COVID-19 pandemic
- Premature end of study due to COVID-19 pandemic
- Permanent end of study intervention due to AE related to COVID-19 infection
- Critical or major protocol deviations due to COVID-19 pandemic

Some safety (adverse events) analyses will also be repeated on the subgroups of safety participants according to trial impact (disruption) due to COVID-19 pandemic (see Section 9.1).

The disposition of screened participants by country and site will be summarized for the screened analysis set using number and percentage.

A summary table to show participant disposition by visit according to trial impact (disruption) due to COVID-19 (visit not done, visit partially done on site, visit partially done by phone and visit done but delayed) will be provided overall and by country for the ITT analysis set.

5.2. Protocol Deviations

All critical or major protocol deviations potentially impacting efficacy analyses (including randomization and drug-dispensing irregularities; see Table 5-1), and other major or critical deviations will be summarized overall and according to COVID-19 impact (i.e., deviations related to COVID-19 pandemic) for the ITT analysis set by study intervention group and overall using number and percentage.

A listing of participants with at least one critical or major protocol deviation will be provided with comprehensive information related to each deviation identified.

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible participant is randomized, b) a participant is randomized based on an incorrect stratum, c) a participant is randomized twice, or d) in a dynamic randomization scheme the study intervention assignment is, in fact, not random, due to a computer program error.

   OR

2. A participant is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a participant at any time in the study is dispensed a different study intervention kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized participant is treated with IMP reserved for randomized participants.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the critical or major irregularities will be categorized and summarized for the ITT analysis set by study intervention group and overall using number and percentage.

Non-randomized, treated participants will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Table 5-1 Randomization and drug dispensing irregularities

Randomization and drug allocation irregularities
• Kit dispensation without IRT transaction • Erroneous kit dispensation • Kit not available • Randomization by error • Participant randomized twice • Forced randomization • Stratification error • Participant switched to another site

6. Demographics and Baseline Characteristics

The demographics, participant characteristics and baseline disease characteristics will be summarized using the ITT analysis set by study intervention group and overall using descriptive statistics or using number and percentage. P-values on the treatment difference for the demographic and baseline characteristics data will not be calculated. In general, no specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety/efficacy analysis.

6.1. Demographics and participant characteristics

The following demographics and participant characteristics will be summarized by study intervention group and overall, both for the ITT and [redacted] sets:

- Age (years)
- Age category (≥18 to <40, ≥40 to ≤65, >65 years)
- Gender (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown)
- Baseline body weight (kg)
- Baseline body weight category (<70, ≥70 to <100, ≥100 kg)
- Baseline height (cm)
- Baseline body mass index (BMI) (kg/m²) derived as: (Weight in kg)/(Height in meters)²

- Baseline BMI category (<15, ⩾15 to <25, ⩾25 to <30, ⩾30 kg/m²)
- Region (Eastern Europe or ROW)
- Smoking status at screening (Never, Current, Former)
- Tobacco consumption at screening: amount (cigarette) per day
- Baseline ICS dose level (Medium, High)

6.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by study intervention group and overall, both for the ITT (except Polysomnography) and [redacted] sets:

6.2.1. Sleep characteristics and sleep related impairment at baseline

- Asthma Sleep Disturbance Questionnaire (sleep disturbance score)*
- PROMIS sleep disturbance Short Form 8a individual T-score and raw score
- Actigraphy
  - [redacted]
  - Wake after sleep onset (WASO)*
  - [redacted]
  - [redacted]
- Sleep diary
  - [redacted]
  - [redacted]
  - WASO*
  - [redacted]
  - Number of nocturnal awakenings*
  - Participants with > 2 weekly average nocturnal awakenings at baseline (Yes, No)*
  - Sleep quality*
  - Restorative sleep*
- [redacted]
- [redacted]

* average value of the assessment reported during the week prior to first IMP intake (or randomization for participants not exposed)

6.2.2. Asthma and associated disease characteristics at baseline

- ACQ-5 and [redacted]
- ACQ-5 in class:
  - (≤3, >3)
  - (≤3.5, >3,5)
- Pre-BD FEV1 (L)
- Pre-BD FEV1 % predicted
- FVC (L)
- FVC % predicted
- [redacted]

- ADSD*
- ANSD*
- [redacted]
- Dos[redacted] level of inhaled corticosteroid (ICS)
- Age of onset of asthma (years)
- Age of onset of asthma (years) in class (<18, ⩾18 to <40, ⩾40)
- Number of severe asthma exacerbation events (identified using LLT) within 1 year prior to the study
- Number of severe asthma exacerbation events (identified using LLT) within 1 year prior to the study (1, 2, >2)
- Number of controller medications at study entry (2 or 3)
- Atopic comorbid condition (Yes, No)
- Participants with Chronic rhinosinusitis with nasal polyps (CRSwNP) co-morbidities (Yes, No)
  Note: CRSwNP will be identified via CMQ10440 coding file provided by Sanofi.

* average value of the assessment reported during the week prior to first IMP intake (or randomization for participants not exposed)

6.2.3. Biomarkers

- Eosinophils counts
- Eosinophils counts in class (<300, ≥ 300 cells/uL)
- [redacted]

6.3. Alcohol, Tobacco and Caffeine Usage

The following alcohol, tobacco and caffeine habits will be summarized on [redacted] analysis set by study intervention group:

- Caffeine consumption: amount (cup) per day reported at Day -1 and Visit 5 (and additional assessment if any)
- Alcohol consumption: amount (glass) per day reported at Day -1 and Visit 5 (and additional assessment if any)
- Tobacco consumption: amount (cigarette) per day reported at Day -1 and Visit 5 (and additional assessment if any)

Caffeine, alcohol, and tobacco consumption will be collected at those visits for [redacted] participants only.

6.4. Medical History

6.4.1. General Medical History

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant.

Medical and surgical history will be coded to "lowest level term (LLT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)", and associated primary "system organ class (SOC)" using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of each database lock.

The number and percentage of participants with any medical history will be summarized by study intervention group and overall and for each primary SOC, HLT and PT both for the ITT and [redacted] analysis sets. The table will be sorted by internationally agreed order of primary SOC, and by alphabetical order of HLTs and PTs. Participants experiencing asthma exacerbations will be further summarized using the LLT level as appropriate within medical history summaries.

Additionally, a separate table will present atopic comorbidities captured in the past and current medical conditions eCRF page by primary SOC, HLT and PT based on the ITT analysis set. Atopic comorbidities will be identified via a file provided by Sanofi containing the following CMQ codes: CMQ10646, CMQ10440, CMQ10540, CMQ10541, CMQ10537, CMQ10076, CMQ10539, CMQ10538.

6.4.2. Disease-Specific History

Not applicable.

6.5. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be presented for the screened analysis set using number and percentage.

7. Study Interventions and Medications

7.1. Prior and Concomitant Medications

The prior and concomitant medications will be presented for the ITT analysis set for each study intervention group (and overall for prior medications) using number and percentage. No statistical test for the between-group difference will be performed.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version in effect at Sanofi at the time of each database lock.

Medications will be summarized by study intervention group according to the WHO-DD, considering the first digit of the anatomic category (ATC) class (anatomic category – Level 1) and the first 3 digits of the ATC class (therapeutic category – Level 2), unless otherwise specified. 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 given medication can be classified as a prior medication as well as a concomitant medication.

The summaries for prior and concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the Dupilumab study intervention group. In case of equal frequency regarding ATCs, alphabetical order will be used.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as described in Section 15.4.3.

7.1.1. Prior Medications

Prior medications are those the participant began prior to first IMP intake. Prior medications can be discontinued before first study intervention administration or can be ongoing during the study intervention phase.

The following prior medication summaries will be generated separately by study intervention group and overall:

- Inhaled corticosteroids, in combination with other controllers summarized by medication type (ICS, LABA, LAMA, LTRA, Other) and standardized medication name.
  Note: These medications are recorded in the Asthma controller medication eCRF page and ATC codes will be used to categorize them into ICS (ATC class R03BA), LABA (ATC class R03AC), LAMA (ATC class R03BB), LTRA (ATC class R03DC) or Other.

- Reliever medications summarized by medication type (SABA, systemic corticosteroids, other) and standardized medication name (see Section 15.10).
  Note: These medications are recorded in the Asthma reliever medication eCRF page.

- Other prior medications.
  Note: These medications are recorded in the Other medication eCRF page.

The prior prohibited medications will also be presented by prohibited medication category as defined in deviation and standardized medication name (see Section 15.10).

7.1.2. Concomitant Medications

Concomitant medications are any treatments received by the participant concomitantly to the IMP, starting from the date of 1st administration of IMP to the date of last administration + 14 days (boundary included).

The following concomitant medications summaries will be generated separately by study intervention group:

- Inhaled corticosteroids in combination with other controllers summarized by medication type (ICS, LABA, LAMA, LTRA, Other) and standardized medication name.
  Note: These medications are recorded in the Asthma controller medication eCRF page and ATC codes will be used to categorize them into ICS (ATC class R03BA), LABA (ATC class R03AC), LAMA (ATC class R03BB), LTRA (ATC class R03DC) or Other.

- Reliever (rescue) medications summarized by medication type (SABA, systemic corticosteroids, other) and standardized medication name (see Section 15.10).
  Note: These medications are recorded in the Asthma reliever medication eCRF page.

- Other concomitant medications.
  Note: These medications are recorded in the Other medication eCRF page.

The concomitant prohibited medications will also be presented by prohibited medication category as defined in deviation and standardized medication name (see Section 15.10).

7.1.3. Post-treatment medications

Post-treatment medications are those the participant took (continued or initiated) in the period running from the 15th day after the last administration of IMP up to the end of the study, based on Investigator's decision. Post-treatment medications will not be summarized or presented in the CSR.

7.2. Study Interventions

The extents of IMP exposure and compliance will be assessed and summarized by actual study intervention group and overall using the safety analysis set.

7.2.1. Extent of Exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as last IMP dose administration date – first IMP dose administration date + 14 days, regardless of unplanned intermittent discontinuations.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, Q1, Q3, minimum and maximum). In addition, duration of IMP exposure will also be summarized categorically by numbers and percentages for each of the following categories:

- >0 and ⩽2 weeks
- >2 and ⩽4 weeks
- >4 and ⩽8 weeks
- >8 and ⩽12 weeks
- >12 weeks

and cumulatively according to the following categories:

- ⩾1 day
- >2 weeks
- >4 weeks
- >8 weeks
- >12 weeks

Additionally, the sum of the duration of IMP (total) exposure for all participants will be summarized by study intervention group and will be expressed in participant years.

7.2.2. Study Intervention Compliance and Modifications

A given administration will be considered non-compliant if the participant did not take the planned dose of study intervention as required by protocol (i.e., a syringe not fully injected is considered as a non-compliant administration). No imputation will be made for missing or incomplete data.

Percentage of compliance for a participant will be defined as the number of administrations that the participant was compliant (planned dose fully injected) divided by the total number of administrations that the participant was planned to take during the study intervention period.

$$\text{Percentage of compliance (\%)} = \left[\frac{\text{Total number of compliant administrations during the study intervention period}}{\text{Number of planned administrations during the study intervention period}}\right] \times 100\%$$

Loading doses for the same participant will be counted as 1 dose.

Percentage of injections with compliance for a participant will be defined as the number of injections that the participant was compliant divided by the total number of injections that the participant was planned to take during the study intervention period.

$$\text{Percentage of injections with compliance (\%)} = \left[\frac{\text{Total number of compliant injections during the study intervention period}}{\text{Number of planned injections during the study intervention period}}\right] \times 100\%$$

Loading doses for the same participant will be counted as 2.

Percentage of compliance and percentage of injections with compliance to the IMP administration will be summarized descriptively as quantitative variables (number, mean, SD, median, Q1, Q3, minimum and maximum). In addition, the percentage of compliance will be presented by the specific ranges for each study intervention group:

- <80%
- ⩾80 %

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose within the intended therapeutic interval (planned treatment period), adjusted according to the tested drug. Cases of symptomatic overdoses will constitute AESIs and will be listed as such. More generally, dosing irregularities will be listed in Section 5.2.

Dose modification of IMP for an individual participant is not allowed and therefore no summary of dose modifications will be provided.

8. Efficacy Analysis

All efficacy analyses will be performed on the ITT analysis set, except for that of the primary efficacy endpoint, which will employ the ITTp set.

Participant will be analyzed for efficacy according to the study intervention group to which they are allocated by the IVRS according to the randomization schedule at the randomization visit (as randomized), irrespective of the study intervention actually received.

For the analysis of primary objective in the treatment period,

- The null statistical hypothesis tested is that there is no mean treatment difference between Dupilumab and placebo on sleep disturbance score in adult participants moderate-to-severe uncontrolled asthma and evidence of Type 2 inflammation.
- The alternative statistical hypothesis tested is that there is a mean treatment difference between Dupilumab and placebo on sleep disturbance score in adult participants moderate-to-severe uncontrolled asthma and evidence of Type 2 inflammation

Note that due to the small sample size of the [redacted], no statistical testing will be conducted for analyses in the [redacted] analysis set. Summary statistics with 95% CI by study intervention group will be provided.

All efficacy measurements collected during the study will be considered for analyses, including those obtained after IMP discontinuation, except if study intervention discontinuation was due to the COVID-19 pandemic; for more details, refer to Table 2-2.

For efficacy endpoints where a change from baseline is assessed, only the participants who have a baseline and at least one post-baseline value available will be included in the analysis (number of participants included in the analysis model reported in the table).

All daily assessments (i.e., asthma sleep disturbance questionnaire, sleep diary) will be analyzed as monthly averages, calculated from the 28 days immediately preceding (and including) the theoretical expected day of the study visit calculated from the day of first IMP intake (note that 28 days is a maximum and that it could be less, in case fewer assessments have been performed within the corresponding 28 days window).

Although actigraphy parameters are assessed daily between Baseline (Day 1) and Week 4, they will be analyzed at each timepoint as weekly averages for the week immediately preceding the study visit, including the day of the visit (same approach for ADSD and ANSD as these data are collected only for each of the 7 days prior the visit [including the day of the visit only for ANSD]).

The other efficacy parameters (spirometry, [redacted], PROMIS, ACQ-5, [redacted] and [redacted]) will not use any of these approach since they are collected/measured a single time before or the day of the visit.

Line plots for change from baseline will be presented by study intervention group, displaying the LS mean and SE at each visit. These plots will be provided for the primary and all secondary continuous endpoints except for [redacted].

When applicable, inferential tests will be performed at all scheduled visits: The adjusted least square (LS) mean in change from Baseline of each study intervention group, the LS mean difference between the dupilumab and placebo groups, and the corresponding SEs and 95% CIs will be provided. The p-value corresponding to the LS mean difference will be provided at Week 12 only.

8.1. Primary Efficacy Endpoint

The primary endpoint is change from baseline in sleep disturbance score at Week 12 assessed using the Asthma Sleep Disturbance Questionnaire.

8.1.1. Primary Analysis

Change from baseline in sleep disturbance score will be analyzed on the ITTp population using a MMRM approach under the Missing at Random (MAR) framework. The MMRM model will include study intervention (Dupilumab, Placebo), age, BMI, stratum (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, rest of world [ROW] with high ICS dose and ROW with medium ICS dose), inclusion in [redacted], visit (up to Week 12), study intervention-by-visit interaction, baseline ACQ-5, baseline sleep disturbance score and baseline-by-visit interaction as covariates.

An unstructured correlation matrix will be used to model the within-participant errors covariances. The Kenward-Roger approximation (**ddfm=kr**) will be used to estimate the denominator of degrees of freedom. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. The adjusted least square (LS) mean in change from baseline of each study intervention group, the LS means difference between the dupilumab and placebo groups, and the corresponding SEs and 95% CI will be provided at all scheduled visits. The p-value corresponding to the LS mean difference will be provided at Week 12 only. For participants discontinuing the study intervention before Week 12 not due to the COVID-19 pandemic, off-study intervention sleep disturbance scores measured up to Week 12 will be included in this analysis. In contrast, for any participants discontinuing the study intervention due to the COVID-19 pandemic, off-study intervention data will not be included (i.e., set to missing) but will be assumed missing at random.

If the MMRM model under unstructured correlation matrix fails to achieve convergence due to complexity of model specification, different covariance structures will be used according to the following order till convergence is achieved:

1. Heterogeneous Toeplitz (TOEPH)
2. Homogeneous Toeplitz (TOEP)
3. First-Order Autoregressive [AR(1)]
4. Compound Symmetry (CS)

8.1.2. Assumption Testing

No assumption testing will be performed.

8.1.3. Missing Data Handling

No imputation will be made for the missing values for the primary analysis, unless specified differently in the estimand strategy (see Table 2-2).

8.1.4. Subgroup Analysis

Primary analysis will be replicated for the following subgroups:

- Age category (⩾18 to <40, ⩾40 years)
- Gender (Male, Female)
- Race (Not-White, White)
- Baseline body weight (<70, ⩾70 to <100, ⩾100 kg)
- Region (Eastern Europe, ROW)
- Participants who had concomitant SCS rescue medications (identified with file provided by Sanofi containing CDGsn00010 medications) (Yes, No)
- Baseline ICS dose level (Medium, High)
- Age of onset of asthma (<18, ⩾18 to <40, ⩾40 years)
- Number of severe asthma exacerbation events (1, 2, >2) within 1 year prior to the study
- Number of controller medications at study entry (2 , 3)
- Smoking history (Former, Never)
- Baseline [redacted]
- Baseline Eosinophils (<300, ⩾300 cells/uL)
- Baseline ACQ-5
    - (≤3, >3,)
    - (≤3.5, >3.5)
- Participants with > 2 weekly average nocturnal awakenings at baseline (Yes, No)
- Participants with Chronic rhinosinusitis with nasal polyps (CRSwNP) co-morbidities (Yes, No)

In these subgroup analyses, nominal p-value will be provided for descriptive purpose only.

Results will also be illustrated with forest plots.

8.1.5. Sensitivity Analysis

A sensitivity analysis on the primary endpoint of change from baseline in average sleep disturbance score at Week 12 will be carried out using an analysis of covariance model (ANCOVA) with data from multiple imputation (MI) on missing scores under an assumption of missing at random (MAR). Under this assumption, each missing score will be imputed 100 times and incorporated with non-missing data to form 100 complete datasets. Each dataset will include average sleep disturbance score at Baseline, Week

4, Week 8, and Week 12, as well as relevant covariates specified below to support the analysis. Following steps will be conducted for this analysis. The number of imputations (100) will be informally verified by replicating sets of 100 imputations and checking whether the combined results are stable. If not stable, the number of imputations will be increased and informally checked as above, until stable estimates are obtained.

- Use the Markov chain Monte Carlo (MCMC) method to impute for intermittent missing values by study intervention group and to create 100 datasets with monotone missing pattern. According to the nature of sleep disturbance score, minimum and maximum values will be specified in this imputation.
- For each of 100 datasets with monotone missing pattern created from MCMC imputation, use monotone regression method to impute the remaining missing value by study intervention group up to Week 12. In the imputation regression model, age, BMI, stratum (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, rest of world [ROW] with high ICS dose and ROW with medium ICS dose), inclusion in [redacted], baseline ACQ-5 score, and baseline sleep disturbance score, will be included as covariates. Change from baseline in sleep disturbance score at Week 12 can be calculated with non-missing score or imputed score for every single participant in all datasets. All 100 datasets with full imputation for missing values will be input to ANCOVA models.
- Repeatedly perform ANCOVA modeling for each of 100 datasets with full imputation for missing values. Change from baseline in sleep disturbance score at Week 12 will be analyzed on the ITTp population in this ANCOVA model, and study intervention (Dupilumab, Placebo), age, BMI, stratum (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, rest of world [ROW] with high ICS dose and ROW with medium ICS dose), inclusion in [redacted], baseline ACQ-5, and baseline sleep disturbance score as covariates.
- The adjusted LS means in change from baseline of each study intervention group, the LS mean difference between the dupilumab and placebo groups, and the corresponding SEs and 95% CI of the differences generated from the 100 ANCOVA models will be combined using Rubin's formula and presented in a statistical table for the ITTp population.

8.1.6. Supplementary Analyses

As a supplementary analysis, the primary analysis will be replicated for the ITT population to investigate the robustness of the results.

Similarly, the primary analysis will be repeated for the ITT population but excluding the first 19 randomized participants, who were accidentally potentially unblinded to study team due to an issue with Interactive Response Technology (IRT), where study intervention arm was wrongly included in the IRT transfer to the IVRS library.

The primary analysis will also be repeated for ITTp population but setting to missing any assessment performed the night following a prohibited medication intake (whichever the prohibited medication and half-life of the product).

Lastly, the primary analysis will also be repeated for ITTp population but setting to missing any assessment performed after SCS intake.

8.1.7. Impact of Covid-19 Pandemic

During the Covid-19 pandemic, a business continuity plan (BCP) was put in place to minimize the impact of the clinic visit interruptions and ensure IMP treatment continuity and data collection. Direct to participant delivery of IMP from the site(s) and home injection(s) done by qualified site personnel and/or health care professionals for study drug administration were made available, where allowed by local regulations and approved by the participant, as planned per protocol. IMP permanent discontinuation due to Covid-19 pandemic is therefore expected to be minimum. Participant reported outcome data are not expected to be missing as they can be completed at the participant's home on his/her electronic devices. Site(s) can update/correct the schedule of completion if visit is rescheduled/delayed – unless site staff cannot access vendor platform to update scheduled dates.

Data missing due to the Covid-19 pandemic are likely to be MAR. Therefore, the primary analysis using MMRM can adequately address this type of missing data. Participant disposition summaries by visit according to trial impact (disruption) due to COVID-19 overall and by country are already mentioned in Section 5.1 of this SAP.

8.2. Secondary and Tertiary/Exploratory Efficacy Endpoints

The secondary and tertiary efficacy endpoints associated with "Change from baseline" (except [redacted], due to limited sample size) will be analyzed using the MMRM model in the same fashion as for the analysis of the primary endpoint (see Table 2-2) with the baseline values corresponding to the outcome variables. Adjusted LS means for each study intervention group, LS mean difference between the Dupilumab and placebo groups, and the corresponding SEs and 95% CIs will be provided for all endpoints (and p-value corresponding to the LS mean difference provided at Week 12 only). However, formal statistical testing will be performed only for the number of nocturnal awakenings and PROMIS t-score that will be performed in the frame of the hierarchical procedure considered to account for multiplicity issues (nominal two-sided p-value provided for descriptive purpose only for other secondary and tertiary endpoints).
Further definitions of endpoints are included in Section 15.8 and Section 15.9.

8.2.1. Sleep diary

In addition to MMRM model, the number of nocturnal awakenings, sleep quality, restorative sleep, [redacted] WASO and [redacted], all based on sleep diary data, will be summarized at baseline and each post-baseline visit (Week 4, Week 8, and Week 12).
The number of nocturnal awakenings will be determined based on the answer on the question 3 from the sleep diary: "Approximately how many times did you wake up last night (not including when you woke up for the day today)?"

8.2.2. Actigraphy data

Duration and patterns of sleep (i.e., [redacted], WASO and [redacted]) will be estimated through a device (Actiwatch) worn on the wrist of the non-dominant hand of the participants, who will complete assessments from Day -11 to Day -1 (right before Day 1); daily assessment thereafter until Week 4; then only the week before a clinical visit until EOT.

In addition to MMRM model, all actigraphy parameters will be summarized through descriptive statistics at baseline and each post-baseline visit (Week 4, Week 8, and Week 12). WASO will be summarized separately to other actigraphy endpoints.

8.2.3. [redacted]

In addition to MMRM model, [redacted] will be summarized through descriptive statistics at baseline and each post-baseline visit (Week 4, Week 8, and Week 12).

8.2.4. Spirometry

For spirometry endpoint (pre-BD FEV1), the MMRM model will also include sex and baseline height as covariates.

In addition to MMRM model, spirometry parameter will be summarized through descriptive statistics at baseline and each post-baseline visit (Week 4, Week 8, and Week 12).

8.2.5. ADSD and ANSD

For both ADSD and ANSD, only the overall score will be presented/assessed and it will be calculated using the average from the 6 items.

In addition to MMRM model, data will be summarized through descriptive statistics at baseline and each post-baseline visit (Week 4, Week 8, and Week 12).

8.2.6. [redacted]

In addition to MMRM model, [redacted] 1-item questionnaire will be summarized through descriptive statistics at baseline and each post-baseline visit (Weeks 4, 8, and 12).

8.2.7. [redacted] in sleep since starting the study intervention

For [redacted] endpoint, the MMRM model will not include baseline value and baseline-by-visit interaction, since no baseline assessment is performed through this questionnaire.

In addition to MMRM model, [redacted] in sleep 1-item questionnaire will be summarized through descriptive statistics at Weeks 4, 8 and 12.

8.2.8. PROMIS Sleep Related Impairment Short Form 8a

In addition to MMRM model, the PROMIS Sleep Related Impairment SF8a t-score and raw score will be summarized at baseline and each post-baseline visit (Week 4, Week 8, Week 12).

8.2.9. Asthma Control Questionnaire [redacted] and ACQ-5)

In addition to MMRM model, the [redacted] global score as well as ACQ-5 score (the mean of the responses to the first 5 questions from the ACQ questionnaire) will be summarized at baseline and each post-baseline visit (Weeks 4, 8 and 12).

ACQ-5 baseline value will be used as a covariate for all MMRM models in the study, except for [redacted]

8.2.10. [redacted]

[redacted] summarized through descriptive statistics only due to the limited sample size of the sub-study.

8.2.11. [redacted]

MMRM model will be performed for the [redacted] concept scores [redacted]). All individual scores should be assessed in

employed participants only, except [redacted] (from question 6) which is not related to work. It will be run as specified generally in the Section 8.2 but without assessment at Week 8.

The [redacted] concept scores will also be summarized at baseline and each post-baseline visit (i.e., Week 4 and Week 12) through descriptive statistics.

In addition, the number and percentage of participants currently employed (yes/no) will be presented at baseline and each post-baseline visit (Week 4 and Week 12) alongside with the number of participants evaluated at those visits.

8.2.12. [redacted]

In addition to MMRM model, [redacted] total score will be summarized at baseline and each post-baseline visit (Week 4, Week 8, Week 12) through descriptive statistics.

8.2.13. Multiplicity issues

In order to handle multiple primary or secondary endpoints, the overall Type-I error will be controlled by the use of a hierarchical inferential approach:

- Statistical significance of the primary analysis at the 0.05 alpha level will be required before drawing inferential conclusions about first secondary endpoint

- Inferential conclusions about successive secondary endpoints will require statistical significance of the prior one.

Hierarchical testing will be performed in the same order as described below:

1. Change from Baseline to Week 12 in the Asthma Sleep Disturbance Questionnaire (primary endpoint)
2. Change from Baseline to Week 12 in the average number of nocturnal awakenings (first secondary endpoint)
3. Change from Baseline to Week 12 in PROMIS t-score

This fixed hierarchical approach will ensure a strong control of the overall Type-I error rate at the 0.05 level.

Additional endpoints (secondary or tertiary) that are not included in the hierarchical testing procedure will not be formally tested (i.e., nominal p-value provided for descriptive purpose only).

9. Safety Analysis

All safety results will be summarized using the Safety analysis set by actual study intervention group.

The observation periods include:

- The **pre-treatment** period is defined as the time from the signed informed consent date up to first administration of the IMP.
- The **treatment-emergent adverse event** (TEAE) period is defined as the time from the first administration of the IMP (on Day 1) to the last administration of the IMP + 84 days or until the participant switches to commercialized dupilumab or other biologics
- The **post-treatment** period is defined as the time starting 1 day after the end of the TEAE period up to the end of the study follow-up.

9.1. Adverse Events

The adverse event types include:

- **Pre-treatment adverse events** are adverse events that developed or worsened or became serious during the pre-treatment period.
- **Treatment-emergent adverse events** are adverse events that developed or worsened or became serious during the TEAE period.
- **Post-treatment adverse events** are adverse events that developed or worsened or became serious during the post-treatment period. AEs categorized as post-treatment AEs (following the rules specified below) will not be summarized.

The primary focus of AE reporting will be on TEAEs. Pre-treatment adverse events will be summarized separately.

All AEs will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of each database lock.

Adverse events will be recorded from the time of signed informed consent until the end of the study or the resolution/stabilization of all SAE and AESI.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment-emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 15.4.4.

Adverse events will be summarized by primary SOC, HLGT, HLT, and PT, sorted by internationally agreed order of primary SOC and then alphabetically for the other levels, for each study intervention group using number and percentage of participants experiencing an adverse event. Multiple occurrences of the same event in the same participant will be counted only once in the tables within an observation period (pre-treatment period or TEAE period). The denominator for computation of percentages will be the safety analysis set within each study intervention group. Participants experiencing asthma exacerbations will be further summarized using the LLT level as appropriate within adverse event summaries.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment or treatment-emergent). For that purpose, the table of all treatment-emergent adverse events presented by primary SOC and PT (sorted by the internationally agreed SOC order and decreasing

frequency of PTs within SOCs in the Dupilumab group) will define the presentation order for all other summaries unless otherwise specified. In case of equal frequency regarding PTs, alphabetical order will be used.

On top of the analysis planned below, all TEAEs, all treatment-emergent SAEs, TEAEs leading to permanent study intervention discontinuation and TEAEs leading to death will be summarized by study intervention group and repeated on the subgroups of safety participants according to trial impact (disruption) due to COVID-19 pandemic.

Overview summary of the number and percentages of participants within the following categories will be provided by study intervention group:

- Any TEAE
- Any study intervention related TEAE
- Any Severe TEAE
- Any Serious TEAE
- Any TEAE leading to permanent study intervention discontinuation
- Any TEAE of special interest
- Any Serious TEAE of special interest
- Any TEAE leading to death

The overview summary for TEAEs will be provided on the safety analysis set and will be repeated on the subgroups of safety participants according to trial impact (disruption) due to COVID-19 pandemic.

Additionally, an overview of pre-treatment AEs will be presented using similar categories including:

- Any AE
- Any Severe AE
- Any Serious AE
- Any AE of special interest
- Any Serious AE of special interest
- Any AE leading to death

Individual listings (AEs, SAEs, TEAEs leading to permanent study intervention discontinuation, AEs leading to death, AESI and all AEs in treated but not randomized participants (where such participants are recorded in the study)) will be provided to support the summary tables based on the safety analysis set. Additionally, any defect in the IMP will be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (i.e., samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether the quality issue must be reported together with an AE or SAE.

No analysis of these data is foreseen. Reporting of these information falls beyond the scope of this SAP.

9.1.1. Incidence of Adverse Events

The following summaries will be generated for the safety analysis set, for each study intervention group.

- All TEAEs presented by primary SOC, HLGT, HLT, and PT, showing the number and percentage of participants with at least 1 TEAE
- All TEAEs presented by primary SOC, showing number and percentage of participants with at least 1 TEAE, sorted by the internationally agreed primary SOC order

- All TEAEs presented by PT, showing number and percentage of participants with at least 1 TEAE, sorted by decreasing incidence of PT in the Dupilumab group
- All pre-treatment AEs presented by primary SOC and PT, showing number and percentage of participants with at least 1 pre-treatment AE
- All TEAEs presented by primary SOC and PT, showing number and percentage of participants with at least 1 TEAE
- All treatment-emergent COVID-19 related adverse events presented by primary SOC and PT, showing number and percentage of participants with at least 1 treatment-emergent COVID-19 related AE
- Common TEAEs (PTs with an incidence $\geqslant$ 5% in any study intervention group) by primary SOC, HLGT, HLT, and PT

9.1.2. Relationship of Adverse Events to Study Intervention

The following TEAE summaries will be generated for the safety analysis set, for each study intervention group.

- All TEAEs by relationship, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE

9.1.3. Severity of Adverse Event

The following TEAE summaries will be generated for the safety analysis set, for each study intervention group.

- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number and percentage of participants with at least 1 TEAE by severity (i.e., mild, moderate, severe).

9.1.4. Serious Adverse Events

The following TEAE summaries will be generated for the safety analysis set, for each study intervention group.

- All serious TEAEs presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 serious TEAE
- All serious TEAEs by relationship, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 serious TEAE

9.1.5. Adverse Events Leading to Permanent Study Intervention Discontinuation

The following TEAE summaries will be generated for the safety analysis set, for each study intervention group.

- All TEAEs leading to permanent study intervention discontinuation, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE leading to permanent study intervention discontinuation

9.1.6. Adverse Events Leading to Study Discontinuation

Not applicable.

9.1.7. Adverse Events of Special Interest (AESI)

As defined in Appendix 15.6, Adverse Events of Special Interest (AESI) include:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Keratitis

- Any severe type of conjunctivitis or blepharitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Significant alanine transaminase (ALT) elevation:
    - ALT >5X the upper limit of normal (ULN) in participants with baseline ALT ⩽2X ULN ("Baseline" refers to ALT sampled at baseline visit or, if baseline value is unavailable, to the latest ALT value before the baseline visit)

    or
    - ALT >8X ULN if baseline ALT >2X ULN
- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP
    - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria
    - In the event of pregnancy in a female participant, IMP should be discontinued.
    - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined
- Symptomatic overdose (serious or nonserious) with IMP/NIMP:
    - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.
    - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined according to the drug label.

The following TEAE summaries will be generated for the safety analysis set, for each study intervention group.

- All TEAEs of Special Interest, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE of Special Interest.
- All serious TEAEs of Special Interest, presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 serious TEAE of Special Interest.

9.1.8. Adverse Events Leading to Death

The following TEAE summaries will be generated for the safety analysis set, for each study intervention group.

- All TEAEs leading to death (death as an outcome on the eCRF form "Adverse Event" as reported by Investigator), presented by primary SOC, HLGT, HLT and PT, showing the number and percentage of participants with at least 1 TEAE leading to death.

9.1.9. Death

The following summaries of deaths will be generated for the safety analysis set, for each study intervention group.

- Number and percentage of participants who died during the trial by study period (i.e., on study, pre-treatment period, TEAE period, post-treatment period, and post-study).
- Number and percentage of participants who died during the trial by cause of death.
- Number and percentage of non-randomized but treated participants or randomized but not treated participants who died (where such participants are recorded in the study).

A listing of all participants who died during the study will be provided.

9.2. Clinical Laboratory Evaluations

The laboratory tests will be performed by the local laboratories according to routine clinical practice at site and country level. The Investigator will review the laboratory report, document this review, and record any clinically relevant findings/changes occurring during the study in the AE section of the CRF.

The following laboratory tests will be performed:

- Hematology: blood eosinophil count
- Highly sensitive (serum at screening and urine at the other visits) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential).
- Hepatitis screening covering hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (total HBcAb); hepatitis C virus antibodies (HCVAb).
- Human Immunodeficiency Virus screening (Anti-HIV-1 and HIV-2 antibodies).
- Tuberculosis test performed only on a country by country basis according to the routine clinical practice and the local guidelines or if required by Regulatory Authorities or Ethics Committees.

Additional laboratory tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations; any clinically significant abnormal lab values will be included in the adverse event analyses. These additional laboratory tests will be displayed in a separate listing.

Eosinophil counts will be summarized for the safety analysis set by study intervention group using descriptive statistics of actual values and change from baseline for each visit or study assessment (baseline and week 12).

9.3. Vital Sign Measurements

Vital signs including weight, heart rate (HR), sitting systolic (SBP) and diastolic blood pressure (DBP), temperature and respiration rate, will be collected at screening visit, at baseline visit (Day 1) before receiving the IMP and then at all subsequent visits.

The vital sign results will be summarized for the safety analysis set by study intervention group using descriptive statistics and for each visit or study assessment (baseline, each-post-baseline time point, last on-treatment value).

The Potentially Clinically Significant Abnormalities (PCSA) at any time during the TEAE period will be summarized for the safety analysis set by study intervention group, using number and percentage. The PCSA are provided in Section 15.7.

All measurements collected during the TEAE period, including values from unscheduled visits, will be considered for the PCSA summaries. The summaries will include participants in the safety analysis set who have at least 1 assessment performed during the TEAE period.

A listing of participants with at least 1 post-baseline PCSA will be provided and will display the participants' profile over time of all vital sign parameters.

Individual data listings will include the following flags:

- Baseline values will be flagged "B",
- Parameter values reaching a PCSA limit will be flagged (+, or - depending on the direction).

9.4. Physical Examination

There will be a complete physical examination at screening, baseline visit and visit 5, to examine and assess any abnormalities that may be present, as indicated by the participant's medical history. It will include (at a minimum) assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Body weight will also be measured at screening, baseline and visit 5 whereas height will be measured at screening only. The weight will be summarized the same way as vital sign parameters, including PCSA description. Results (normal, abnormal, or not done) from the assessment will be reported. All deviations from normal will be recorded, including those attributable to the participant's disease.
Any new or worsening finding will be reported as a new adverse event.

9.5. Electrocardiogram

12-lead ECG will be obtained at SV1 using an ECG machine that automatically calculates HR (Heart Rate) and measures QRS duration and PR and QT intervals.

A summary of ECG overall interpretation at baseline (abnormal/normal) will be presented for the safety analysis set.

9.6. Other Safety Data

Not applicable.

10. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

11. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

12. Interim Analysis

An interim analysis (IA) in the study is planned for the purpose of [redacted] when approximately 50% of participants (approximately 130 participants from the ITTp population and n_1 =117 evaluable participants) have completed the Week 12 visit or discontinued the study. The sample size re-estimation is planned to mitigate risk of power loss in the primary MMRM analysis described in Section 8.1.1, given the large variability of placebo effects observed in [redacted]. The IA will be performed according to the [redacted] summarized as follows:

- Let $\widetilde{n_2}$ be the incremental sample size between Stage 1 and Stage 2 (viz., up to and after the IA, respectively), and the cumulative sample size up to and including Stage 2 (final analysis) be $n_2 = n_1 + \widetilde{n_2}$.
- The sample size re-estimation will be performed based on the [redacted]
- [redacted]

- [redacted] No additional IA will be performed in the case of sample size increase. The test statistic at the final analysis will not be adjusted, since no sample size increase is planned if that [redacted]
- There is no plan to stop the trial early for superiority at the IA, and therefore the type I error can be preserved in theory. To implement a conservative analysis, an administrative alpha of 0.001 will be spent at the interim and 0.049 will be reserved for the final analysis.

13. Changes in the Planned Analysis

13.1. Nocturnal Awakenings Average

Protocol specifies that the analysis of the Change from Baseline on average number of nocturnal awakenings from Sleep Diary data is to be performed on a weekly average. In final analysis this will be performed on a monthly average (28 days preceding the visit).

13.2. Study Intervention Discontinuation Due to Covid-19 Handling in Primary Analysis

Protocol states that in MMRM analysis of the primary endpoint, participants discontinuing study intervention prior to Week 12 will have all data included as part of the model, including off study intervention sleep disturbance scores. In SAP it is clarified that participants who experienced study intervention discontinuation due to Covid-19 pandemic will have off-study intervention sleep disturbance data set to missing and not included in the model.

13.3. Safety Analysis Set

The definition of the safety analysis in the protocol has been expanded in the SAP to only include randomized participants.

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15. Appendices

15.1. Summary of Statistical Analyses

Endpoint	***Analysis Set***	***Primary analysis***	***Sensitivity and Supportive analysis***	***Subgroup analysis***	***Estimands***
Primary endpoint					
Sleep Disturbance score: change from baseline to week 12 (Dupilumab, placebo)	*ITTp*	*MMRM (missing data handled through the MMRM model only, no additional imputation performed)*	*Sensitivity analyses: Repeat of Primary analysis based on multiple imputation analysis.* *Supplementary analyses: Repeat of Primary analysis four times: one for ITT population and one for ITT population excluding first 19 randomized participants due to IRT issue, one for ITTp population setting to missing any assessment performed the night following a prohibited medication intake, and one for ITTp population setting to missing any assessment performed after SCS intake.*	*Yes*	*Yes*
Secondary endpoints					
Continuous variables	*ITT*	*Same approach as primary endpoint*	*No*	*No*	*Yes (only for secondary endpoints included in the hierarchical testing procedure)*

Endpoint	*Analysis Set*	*Primary analysis*	*Sensitivity and Supportive analysis*	*Subgroup analysis*	*Estimands*
Tertiary/Exploratory endpoints					
[redacted]					

15.2. Schedule of Study Procedures

Procedure	Screening		Intervention Period (weeks)[a]					Follow-up (up to 12 weeks after last IMP dose)[b]	Notes
	D-35 to D-12	D-11	W0 (D1)	W4 ±3 days	W8 ±3 days	W12 ±3 days	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[c] • ESD = early study discontinuation[d]
Visit	SV1[e]	SV2[e]	V2	V3	V4	V5 (EOT)		V6 (EOS)	SV1, SV2, V2-V5: on-site visits; V6: phone visit. For the participants who switch to commercialized dupilumab (or other biologic product), the call visit should be done prior to the first injection with commercialized dupilumab (or other biologic product).
Informed consent	X								
Inclusion and exclusion criteria	X		X						
Demography	X								
Complete physical examination including height and weight	X		X			X	X		A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems. Body weight (kg) will be measured at SV1, V2, and V5. Height (cm) will be measured only at SV1.
Vital signs	X		X	X	X	X	X		Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius)
Medical history (includes substance usage)	X								Substances: tobacco usage collected at screening; alcohol usage will be collected in case of ALT increase
Past and current medical conditions	X								It will also include atopic comorbidities (eg, AD, CRSw/sNP) and a question about the weekly average nocturnal awakenings due to asthma symptoms in the week before SV1
Reversibility test	X[f]								Only required if a reversibility test meeting eligibility criterion was not performed within 6 months prior to SV1
Serum pregnancy test (WOCBP only)[g]	X								

Procedure	Screening		Intervention Period (weeks)[a]					Follow-up (up to 12 weeks after last IMP dose)[b]	Notes
	D-35 to D-12	D-11	W0 (D1)	W4 ±3 days	W8 ±3 days	W12 ±3 days	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[c] • ESD = early study discontinuation[d]
Urine pregnancy test (WOCBP only)[g]			X	X	X	X	X	X	
Hepatitis B and C screening, HIV screening, TB screening[h]	X								
12-lead ECG	X								
Eosinophil count	X[i]		X			X	X		
IVRS/IWRS call	X		X	X	X	X	X	X	
Randomization			X						
Study intervention administration[j]			←=======Q2W after D1=======→						
Study intervention dispensation			X	X	X	X			
Home dosing diary[k]			X	X	X	X	X		Paper diary
Asthma background therapy diary[k]			X	X	X	X	X		Paper diary
[redacted]	X[l]		X	X	X	X	X		[redacted] should be conducted prior to spirometry and the participant should refrain from eating and drinking for ≥1 hour before the procedure.
Spirometry (Pre-BD FEV_1)[m]	X[n]		X	X	X	X	X		
Patient assessments (at home)									
Asthma Sleep Disturbance Questionnaire		←==========daily==========→							Electronic devices; Baseline sleep disturbance scores will be the mean scores recorded for the 7 days prior to randomization.

Procedure	Screening		Intervention Period (weeks)[a]					Follow-up (up to 12 weeks after last IMP dose)[b]	Notes
	D-35 to D-12	D-11	W0 (D1)	W4 ±3 days	W8 ±3 days	W12 ±3 days	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[c] • ESD = early study discontinuation[d]
Sleep Diary		←==========daily==========→							Electronic devices
Actigraphy[e]		X	X	X	X	X	X		Further details on the procedure will be provided in a separate instruction manual
ADSD (Asthma Daytime Symptoms Diary)		X	X	X	X	X	X		Electronic devices: completed by the patient for 7 days prior to the visit, every 4 weeks. The device will be provided to participants at SV2.
ANSD (Asthma Nighttime Symptoms Diary)		X	X	X	X	X	X		Electronic devices: completed by the patient for 7 days including the visit day, every 4 weeks. The device will be provided to participants at SV2.
Patient assessments (at clinic)									
[redacted][p]	X		X	X	X	X	X		Electronic devices
[redacted]			X			X			Type II home[redacted] devices
[redacted]			X	X	X	X	X		Electronic devices
[redacted]				X	X	X	X		Electronic devices
PROMIS–Sleep Related Impairment 8a scale on sleep			X	X	X	X	X		Electronic devices
[redacted]			X	X	X	X	X		Electronic devices

Procedure	Screening		Intervention Period (weeks)[a]					Follow-up (up to 12 weeks after last IMP dose)[b]	Notes
	D-35 to D-12	D-11	W0 (D1)	W4 ±3 days	W8 ±3 days	W12 ±3 days	E/D		E/D=Early Discontinuation including: • ETD = early treatment discontinuation[c] • ESD = early study discontinuation[d]
[redacted]			X	X		X	X		Electronic devices
AE, SAE, AESI	←==========							==========→	AE, SAE and AESI will be collected as of SV1
Prior and concomitant medication review	X	X	X	X	X	X	X	X	
Device deficiencies			X	X	X	X	X		This refers to prefilled syringes

a In exceptional situations when the participant cannot attend an on-site visit during the intervention period, the visit can be performed remotely ensuring at least the procedures that can be done at home: PROs completion, actigraphy, home [redacted] if applicable, IMP administration, blood samples collection, pregnancy test, if applicable, safety reporting, and concomitant medications.

b **Post-treatment Follow-up**: up to 12 weeks or until the participant switches to commercialized dupilumab (or other biologic product), whatever comes first.

c **ETD**: Participants who prematurely discontinue the study intervention (prior to completing the 12-week treatment period) should attend an ETD visit at earliest convenience with all the assessments planned for the EOT visit (Visit 5), except IMP. In particular cases when the ETD visit is close to a regular study visit, ETD could be merged and will replace the regular visit. In addition, the participants will be asked and encouraged to complete all the remaining study visits according to the visit schedule until and including the EOT visit (Visit 5). Under exceptional circumstances when a participant cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and concomitant medications should be collected.

d **ESD**: Participants who prematurely discontinue the study during the intervention period should attend an ESD visit at earliest convenience with all the procedures planned for the EOT Visit (Visit 5) except IMP. Under exceptional circumstances when a participant cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs and, concomitant medications should be collected.

e If preferred by the participant and the investigator for logistic reasons, screening visit 1 (SV1) and screening visit 2 (SV2) can be merged into a single on-site visit. Importantly, this single screening visit will have to be done on Day -11.at the latest.

f 3 attempts may be performed during the screening period to meet the qualifying criteria for reversibility before randomization.

g Serum pregnancy test at screening visit (SV1) and urine pregnancy tests at the other visits using dipstick. A WOCBP must have a negative highly sensitive pregnancy test at SV1 (serum pregnancy test) and on Day 1 before the first dose of study intervention (urine or serum, if required by local regulations). If a urine test on Day 1 cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. In case of positive urinary test during the study, a serum pregnancy test should be performed as soon as possible to confirm the pregnancy. A urine pregnancy test will be performed at home at the follow-up visit.

h Hepatitis screening covering hepatitis B surface antigen (HBs Ag), total hepatitis B core antibody (total HBcAb); hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative) and HBcAb (positive), HBV DNA testing will be performed to rule out a false positivity or to clarify the serological status if the Investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCVAb (positive), HCV RNA testing may be performed to rule out a false positivity. Human Immunodeficiency Virus screening (Anti-HIV-1 and HIV-2 antibodies). Tuberculosis testing will be performed only on a country-by-country basis according to the routine clinical practice and the local guidelines if required by Regulatory Authorities or Ethics Committees.

i Retesting of eosinophil count is allowed up to three times during the screening period to meet inclusion criteria for showing eosinophil count ≥150 cells/microliter cells/mL (details in Protocol I 04) before randomization. This is only required if the participant doesn't have the blood eosinophil count measured within 6 months prior to SV1 in the absence of OCS treatment.

j Investigational product administrations (Q2W) should be separated by at least 11 days. The administration is performed on site during planned visits alternating with Q2W home administration (participant, caregiver, or health care professional) or in a health care facility. On Day 1, loading dose as follows: 400 mg dupilumab for the dupilumab arm (200 mg x 2 syringes injections) and 2 placebo syringes for the placebo arm.

k Should be completed by participants regularly to record investigational (home dosing diary) and non-investigational (asthma background therapy diary) product information. Recorded data will be collected by the investigator at each on-site visit.

l Retesting of [redacted] can be performed one additional time during screening if the eligibility criterion for [redacted] was not met at SV1. [redacted] will be re-checked at randomization visit (V2) for eligibility. It will be performed after a wash-out period of bronchodilators according to their action duration. Further details on the procedure will be provided in a separate instruction manual.

m Spirometry test should be performed before IMP administration, in the morning if possible. If testing can only be done at another time during the day, then the testing should be done at approximately the same time of day at each visit throughout the study. Spirometry will be performed after a wash-out period of bronchodilators according to their action duration. This will be verified before performing the measurements. For spirometry the investigator will assess the eligibility based on the FEV_1 local values from SV1 and Visit 2 before randomization (the results from central reading will not be available on the same day). Further details on the procedure will be provided in a separate instruction manual.

n A participant who is unable to complete a successful spirometry effort as defined by 2005 ATS criteria or evaluated by the investigator can be retested one additional time during the screening period of the study.

o Actigraphy: The participants will complete baseline assessments from Day -11 to Day -1 (right before Day 1); daily assessment thereafter until Week 4; then only the week before a clinical visit until EOT. Baseline value will be calculated using the data from Day -7 to Day -1.

p [redacted]

q Each participant in this substudy will have a total of 2 overnight [redacted] 1 overnight [redacted] using Type II home devices on Day -1 to collect baseline data and 1 more at Week 12. If the sleep recording is inadequate as judged by the central reading site, the at-home sleep assessment will be repeated within 1 week of the original assessment.

ACQ-5: Asthma Control Questionnaire-5; [redacted] AD: atopic dermatitis; ADSD: Asthma Daytime Symptoms Diary; AE: adverse event; AESI: adverse event of special interest; ALT: alanine transaminase; ANSD: Asthma Nighttime Symptoms Diary; [redacted] ATS: American Thoracic Society; BD: bronchodilator; CRSw/sNP: chronic rhinosinusitis with/without nasal polyps; D: day; E/D: early discontinuation; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; ESD: early study discontinuation; ETD: early treatment discontinuation; [redacted] FEV_1: forced expiratory volume; HBcAB: hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HCVAb: hepatitis C virus antibody; HIV: human immunodeficiency virus; IMP: investigational medicinal product; IVRS: interactive voice response system; IWRS: interactive web response system; OCS: oral corticosteroid; [redacted] ; PRO: patient-reported outcome; PROMIS: patient-reported outcome measurement information system; [redacted] ; RNA: ribonucleic acid; SAE: serious adverse event; TB: tuberculosis; W: week; F WOCBP: woman of childbearing potential; [redacted]

15.3. Missing Efficacy Data

ADSD and ANSD

Global score to be calculated if both conditions meet

- There are at least 4 items (out of 6) available at each day.
- There are at least 4 days available to calculate the average weekly score. For post baseline visits, if less than 4 measurements are available from the 7 days prior the visit [including the day of the visit for ANSD]), the most recent 4 measurements from the 11 days prior the visit will be used for the calculation; if finally, less than 4 measurements are available, it will be considered as missing.

[redacted]

- A given score cannot be calculated if there is at least one response used for the calculation that is missing.
- Responses from other assessments should not be used to impute missing data. For example, if a participant indicated that he worked 40 hours at one assessment, but left that question blank on another assessment, the blank response should remain missing.
- If the participant entered a range of hours, the midpoint should be considered for the analysis.

Asthma Control Questionnaire [redacted] and ACQ-5)

- Based on the manual of ACQ (2), any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing score, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. For instance, answer to question 5 is missing at Visit 4, and all questions are completed at Visit 3. Then the question 5 score at Visit 4 is interpolated as: (sum of score at Visit 4/sum of scores excluding question 5 at Visit 3) × score of question 5 at Visit 3. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

[redacted]

- To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For responses with more than acceptable amount of missing value(s), the overall score will be considered as missing. For responses with amount of missing value(s) within accept range, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ.

Other Participant-Reported Outcomes

For all other questionnaires, if one or more questions are left unanswered, the questionnaire is not scored.

No imputation will be made for the missing values.

15.4. Missing Safety Data

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

15.4.1. Handling of missing age

If age is missing but year of birth is collected, then age will be derived as year of informed consent signed minus year of birth.

15.4.2. Handling of computation of study intervention duration if investigational medicinal product end of treatment date is missing

For the calculation of the study intervention duration, the date of the last dose of IMP is equal to the date of last administration reported on the eCRF "Treatment status" page. If this date is missing, the last available administration date in the "Exposure" form will be used.

The last dose intake should be clearly identified in the eCRF and should not be approximated by the last returned package date.

15.4.3. Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

15.4.4. Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

15.4.5. Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.
The last dose intake should be clearly identified in the eCRF and should not be approximated by the last returned package date.

15.4.6. Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of related adverse events, but no imputation should be done at the data level.

15.4.7. Handling of missing severity/grades of adverse events

If the severity/grade is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

15.4.8. Handling of potentially clinically significant abnormalities

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

15.5. Visit Windows

The analysis window below "[in brackets]" will be applied to post-baseline measurements to allocate them to a scheduled visit for the parameter (see Appendix 15.2 for details of scheduled visits).

Table 15-1 Analyses window definition

Scheduled visit post baseline	Targeted study day* **	[redacted]/Weight/ Eosinophil parameters	[redacted] parameter	Diary data (Asthma sleep disturbance questionnaire/ Sleep diary)	All other parameters
Week 4 (Visit 3)	29		[2, 56]	[2, 29]	[2, 42]
Week 8 (Visit 4)	57			[30, 57]	[43, 70]
Week 12 (Visit 5)	85	[2, ∞]	[57, ∞]	[58, ∞]	[71, ∞]

* The reference day (denoted as Day 1) for the calculation of study day will be the day of the first administration of IMP (except for participants randomized but not exposed). (See Section 4.4.6).
** For actigraphy data as well as for ADSD/ANSD parameters, each post-baseline assessment will be allocated to a scheduled visit, taking into account **the day of the corresponding actual visit on site**. For other parameters (daily collected or collected once per visit) each post-baseline assessment will be allocated to a scheduled visit, taking into account **the day of the assessment**.

After applying the above time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. In case of equality, the last measurement will be used. Re-allocated scheduled visits (i.e., visit numbers) should be sequential if ordered by the date of measurement.

If there is no measurement available for a given parameter in an analysis window data, is considered missing for the corresponding visit.

15.6. Search Criteria for AESI

Table 15-2 Search Criteria for AESI

AESI	Search Criteria
Anaphylactic reactions	SMQ: Anaphylaxis [Narrow]
Systemic hypersensitivity reactions	SMQ: Hypersensitivity [Narrow]
Helminthic infections	HLTs of "Helminthic infections NEC"
Keratitis	PTs of • Keratitis, Allergic keratitis • Ulcerative keratitis • Atopic keratoconjunctivitis • Herpes ophthalmic • Ophthalmic herpes simplex

Any severe type of conjunctivitis or blepharitis	1. Narrow conjunctivitis is defined as the following PTs • Conjunctivitis • Conjunctivitis allergic • Conjunctivitis bacterial • Conjunctivitis viral • Atopic Keratoconjunctivitis 2. Broad conjunctivitis is defined as the following PTs • Conjunctivitis, Conjunctivitis allergic • Conjunctivitis bacterial • Conjunctivitis viral • Atopic Keratoconjunctivitis • Blepharitis • Dry eye • Eye irritation • Eye pruritus • Lacrimation increased • Eye discharge • Foreign body sensation in eyes • Photophobia, Xerophthalmia • Ocular hyperaemia • Conjunctival hyperaemia 3. Conjunctivitis is defined as the following PTs • Conjunctivitis • Non-infective conjunctivitis • Conjunctivitis allergic • Conjunctivitis bacterial • Conjunctivitis viral • Eye irritation • Eye inflammation
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	CMQ10641 based on HLT=Eosinophilic disorders or PT=Eosinophil count increased followed by blinded medical review for selection of relative events
Significant ALT elevation	- ALT >5 × the ULN in participants with baseline ALT ⩽2 × ULN or - ALT >8 × ULN if baseline ALT >2 × ULN
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP	“Pregnancy” or “Partner Pregnancy” checked in eCRF form “Pregnancy”

Symptomatic overdose (serious or nonserious) with IMP/NIMP	"Overdose of Study Treatment" or "Overdose of NIMP" checked and "Symptomatic overdose" checked in eCRF form "Overdose"

15.7. Potentially Clinically Significant Abnormalities (PCSA) Criteria

Table 15-3 Potentially Clinically Significant Abnormalities Criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

(From BTD-009536 May 21, 2014)

Parameter	PCSA	Comments
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 ≥20mmHg ≥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.
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007

15.8. Participant-Reported Outcomes (PROs)

Asthma Sleep Disturbance Questionnaire

The Asthma Sleep Disturbance Questionnaire is a PRO measure designed to assess the impact of asthma on participants' sleep. Scores range between 0 to 4 with 0 indicating no impact of asthma on sleep and 4 indicating higher impact of asthma on sleep.

Participants will be instructed to record the severity of the disturbance of their sleep due to asthma as follows:

- 0 = Slept through the night, no asthma symptoms,
- 1 = Slept well, no nighttime awakenings because of asthma, but some asthma symptoms in the morning,
- 2 = Woke up once because of asthma (may or may not include early awakening),
- 3 = Woke up several times because of asthma (may or may not include early awakening),
- 4 = Bad night, awake most of the night because of asthma.

The participants will record their sleep disturbance in an electronic diary, once a day upon awakening.

Asthma Sleep Disturbance Questionnaire data will be provided by CLARIO.

ADSD and ANSD

ADSD and ANSD assess asthma severity based on participant self-report of asthma core symptoms (i.e., difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain and cough).
Both ADSD and ANSD are composed of 6 items rated using an 11-point numeric rating scale (NRS) that ranges from 0 = None to 10 = as bad as you can imagine, which will be completed by participants daily for 11 days before Baseline visit and for 7 days prior each subsequent visit (every night before they go to bed for ADSD and every morning when getting up for ANSD, respectively).

ADSD and ANSD data will be directly provided by CLARIO.

[redacted]

PROMIS Sleep Related Impairment Short Form 8a

The PROMIS is a DSM-5, Level 2, sleep disturbance measure to assess the impact of sleep-related impairment during waking hours. This study uses the 8-item PROMIS Sleep Related Impairment Short Form (PROMIS SF v1.0 Sleep-Related Impairment Short Form 8a).

The questionnaire focuses on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. Though Sleep-Related Impairment does not directly assess cognitive, affective, or performance impairment, it does measure waking alertness, sleepiness, and function within the context of overall sleep-wake function. It assesses sleep-related impairment over the past seven days. Each item is rated on a 5-point scale (1 = not at all; 2 = a little bit; 3 = somewhat; 4 = quite a bit; and 5 = very much) with a range in score from 8 to 40 with higher scores indicating greater sleep impairment.

PROMIS raw score is calculated by summing the answers to the 8 items on the short form. All questions must be answered in order to produce a valid score using the scoring tables. PROMIS raw score and T-score will not be calculated if there is no answer for at least one item.
Locate the applicable score conversion in Table 15.8.1, and use this table to translate the total raw score or imputed total score into a PROMIS T-score for each participant. The T-score rescales the raw score into a

standardized score with a mean of 50 and a standard deviation of 10. Therefore, a person with a T-score of 40 is one SD below the mean. The standardized T-score is reported as the final score for each participant.

Table 15.8.1 PROMIS Sleep-Related Impairment conversion table

Raw Score	T-score	Raw Score	T-score
8	30	25	60.3
9	35.1	26	61.3
10	38.7	27	62.3
11	41.4	28	63.3
12	43.6	29	64.3
13	45.5	30	65.3
14	47.3	31	66.3
15	48.9	32	67.3
16	50.3	33	68.4
17	51.6	34	69.5
18	52.9	35	70.7
19	54	36	71.9
20	55.1	37	73.3
21	56.1	38	75
22	57.2	39	76.9
23	58.2	40	80
24	59.3		

PROMIS score will be directly provided by CLARIO.

Sleep diary

Collected daily including 11 days immediately preceding the baseline visit (V2), and daily for 12 weeks (until end of study intervention).

A sleep diary is designed to gather information about participant's daily sleep pattern. Participants are instructed to complete all questions upon awakening each day.

The Sleep Diary is composed of seven generic, participant-reported questions that assess sleep concepts of relevance and importance to adults who report sleep disturbance due to asthma.

The Sleep Diary features two subjective, participant-rated items that use a 0-to-10 NRS to assess sleep quality and feeling rested upon awakening (i.e., restorative sleep). Additional items include the participant-estimated initial sleep attempt time and sleep onset time, number of nighttime awakenings after sleep onset, total time spent awake after sleep onset, and wake time the next day. All questions except the one about

restorative sleep ask participants to recall "last night"; question about restorative sleep asks participants to recall "when they got up for the day today". Items about sleep quality and restorative sleep are scored; the other items are reported/described separately, as appropriate for each item.

The following variables will be derived from sleep diary:

WASO (min)= Time awake after initial sleep onset but before the final awakening

This is data collected from Question 3 of the Sleep Diary: "Considering all the times you woke up last night, how much time were you awake in total?"

[redacted]

Sleep diary data will be directly provided by CLARIO.

Asthma Control Questionnaire ([redacted] and ACQ-5)

[redacted] collects participants assessment of their asthma during the previous week based on 6 questions on a 7-point scale (0 = no impairment to 6 = maximum impairment). [redacted]

The ACQ was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of study intervention. The [redacted], with the first 5 items assessing the most common asthma symptoms (corresponding to ACQ-5):

1. frequency in past week awoken by asthma during the night
2. severity of asthma symptoms in the morning
3. limitation of daily activities due to asthma
4. shortness of breath due to asthma
5. wheeze

[redacted]

[redacted]

A global score is calculated as follows: [redacted] Higher score indicates lower asthma control. Participants with a score below 1.0 reflect adequately controlled asthma and participants with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the [redacted], a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.
The participants will complete the [redacted] as per SoA.

ACQ-5 score is the mean of the first 5 questions and, therefore, ranges between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Participants with a score below 1.0 reflect adequately controlled asthma and participants with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the MCID.

At screening and randomization, ACQ-5 scores (the mean of the responses to the first 5 questions) will be derived from [redacted]. For the statistical analysis, centrally read values of pre-BD FEV1 will be used.

[redacted] and ACQ-5 data will be provided by CLARIO.

[redacted]

[redacted]

15.9. Clinician-Reported Outcomes (CLINROs)

15.9.1. Clinician Assessments

[redacted]

Spirometry

A spirometer that meets the 2005 ATS/European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with these recommendations.
For prebronchodilator measured parameters, including FEV1 and forced vital capacity (FVC), spirometry will be performed before IMP administration and after withholding the standard of care asthma treatment as detailed in the clinical trial protocol which will be verified before performing the measurements.

For post-bronchodilator FEV1, the measurement should follow the steps as that at screening test for reversibility validation.
At all visits, spirometry should be performed before IMP administration, in the morning, if possible. The spirometer provided by the service provider should be used and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements. Afternoon/evening is allowable in the exceptional circumstance when morning spirometry cannot be performed. Spirometry should be done at approximately the same time at each visit throughout the study.
Pulmonary function tests will be measured in the sitting position if possible. If the testing was made with the participant in another position, this should be noted on the spirometry report. For any participant, the position should be consistent throughout the study.
Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at each visit. The acceptability criteria must be applied before the repeatability criteria.
Unacceptable maneuvers must be discarded before applying the repeatability criteria. At least 2 acceptable curves must be obtained.
The largest FEV1 and largest FVC should be recorded after the data from all of the acceptable curves have been examined, even if they do not come from the same curve.
The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a participant is seen and subjected to spirometry. The calibration records should be kept in a reviewable log. It is preferred that the equipment that is used to calibrate the spirometer (ie, 3-liter syringe) be subjected to a validated calibration according to the manufacturer's specifications. A participant who is unable to complete a successful spirometry effort as defined by ATS criteria or evaluated by the investigator or who didn't meet the eligibility criterion at SV1 can be retested one additional time during the screening period of the study. The spirometry will be centrally read.

Spirometry data will be provided by CLARIO.

Reversibility test

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Participants will receive 2 to 4 puffs of albuterol/salbutamol from a primed metered dose inhaler (MDI). Alternatively, and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. Reversibility, which is defined as an increase in absolute FEV1 of $\geqslant$12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration. If the participant does not meet the reversibility at SV1, up to 3 repeat attempts can be performed at any time during screening, prior to the randomization visit (Visit 2). This is only required if a reversibility test meeting eligibility criterion was not performed within 6 months prior to SV1.

15.9.2. Center Assisted Assessments

[redacted]

[redacted] Actigraphy data

Wrist actigraphy is a technique for measuring movement of a limb over an extended recording period (days to weeks). The signals generated by wrist movement are sensed by a tiny microcomputer contained within the watch (See Protocol Section 8.1.1) and translated into activity counts.

The device (Actiwatch) is being worn on the wrist of the non-dominant hand in this study to provide estimates of the duration, timing, and patterns of sleep in study participants (i.e., [redacted], WASO, and [redacted]). Eligible participants will be trained on how to use the Actiwatch and will complete assessments from Day -11 to Day -1 (right before Day 1); the assessments performed at the same date as Day 1 will be taken into account for baseline calculation only if the end time of assessment is before 12 pm, reflecting the last night before the visit; daily assessment thereafter until Week 4; then only the week before a clinical visit until EOT.

An operational manual will be provided to the Investigators.

Actigraphy data score will be directly provided by KONEKSA.

15.10. Rescue and Prohibited Medications.

Rescue medications (i.e., reliever medications) will be identified from the "Asthma Reliever Medication" eCRF page.

In the table summary, rescue medications will be categorized into SABA (ATC class R03AC), systemic corticosteroids (ATC class H02AB) or Other.

Treatment with following medications is considered as prohibited prior to the first IMP intake (including prior the study entry) and when taken concomitantly with the IMP:

- Any biologic therapy (including experimental treatments) or systemic immunosuppressive drugs

- Treatment with systemic corticosteroids (systemic corticosteroids can only be used to treat an asthma exacerbation, and are not allowed to be used for other conditions)*
- Live (attenuated) vaccine**
- Sedative, anxiolytic, or hypnotic treatments (including melatonin)
- Systemic sedative antihistamines (except the newer generations of antihistamines like cetirizine, loratadine and fexofenadine)
- Theophylline
- Lipophilic beta blockers, Opioids, Clonidine, Antidepressants or other medications known to interfere with sleep***

* For participants recruited before protocol amendment 1, systemic corticosteroids intake is considered as prohibited. For other participants, systemic corticosteroids used to treat an asthma exacerbation are allowed and recorded (i.e., considered as rescue medication, not prohibited).
** Also considered as prohibited after the last IMP intake, up to the end of the study.
*** Note: In most cases, chronic treatments administered regularly and at stable dosing are acceptable. Investigators should assess the degree to which an individual medication may cause changes in sleep pattern or sleep quality during the study, compared to the pre-baseline state.

16. SIGNATURE PAGE

Client:	**SANOFI**
Protocol Number:	LPS16677
Document Description:	Final Statistical Analysis Plan
SAP Title:	A Phase 4, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of the effect of dupilumab on sleep disturbance in patients with uncontrolled persistent asthma
SAP Version Number:	2.0
Effective Date:	24 FEB 2022

Author(s):

[redacted]

Approved by:

[redacted]

[redacted]

ADDENDUM TO STATISTICAL ANALYSIS PLAN FOR LPS16677

The SAP was approved in February 2022. Due to data issues detected during the course of the study, this addendum provides additional data handling rules not included in the SAP approved.

#1 In Section 15.8 of SAP: Handling rule of duplicates records for daily questionnaires

There are many duplicate records for daily questionnaires remotely completed by phone (Asthma sleep disturbance questionnaire/sleep diary/ANSD/ADSD). The duplicates (same participant, question, date, but with different time/answer provided) will have to be managed at ADaM level.

The rule to select the most appropriate record is as the followings:

1. To select the most frequently recorded response for a given patient/question/day.
2. If it does not enable to identify a unique response (eg, 2 different answers submitted 2 times), then the earliest submission (based on recorded time) will be selected.

#2 In Section 15.8 of SAP: Handling of Sleep Diary Data

Sleep diary is one of the PRO questionnaires in LPS16677 with the following questions:

1: Select the number that best describes the quality of your sleep last night
2a: Approximately what time did you start trying to fall asleep last night?
2b: Approximately what time did you fall asleep last night?
3. Approximately how many times did you wake up last night (not including when you woke up for the day today)? Record "0" if you do not remember waking up last night.
4. Considering all the times you woke up last night, how much time were you awake in total? Record "0" if you do not remember waking up last night.
5: At what time did you wake up for the day today?
6. Select the number that best describes how rested you felt when you got up for the day today.

During the ongoing blinded data review, illogical/inconsistent responses to these questions have been identified within the same participant and questionnaire submission. For example, time falling asleep is recorded to occur before trying to fall asleep, time waking up is recorded to occur before time of falling asleep, total sleep time is recorded as being longer than the time in bed, etc.

In order to remove the illogical responses in the derivation of sleep related endpoints, the following rules will be applied:

A. For questions related to previous night (2a and 2b), if the recorded time lies between 12:00 and 23:59 then set the date equal to the day before the questionnaire was completed. Otherwise set date equal the day questionnaire was completed.
B. Additionally, the following conditions will be checked:
    1. "Date/Time Did You Wake Up Today" must be equal or later than "Date/Time Fall Asleep Last Night"
    2. "Date/Time Did You Wake Up Today" must be later than "Date/Time Try Fall Asleep Last Night"

3. "Date/Time Did You Wake Up Today" minus "Date/Time Fall Asleep Last Night" must be equal or greater than WASO which is "Time awake after initial sleep onset but before the final awakening" and is the response to Question 4.
4. "Date/Time Fall Asleep Last Night" must be equal or later than "Date/Time Try Fall Asleep Last Night"
5. WASO is equal or greater than zero.

If any of the above conditions fail, then the data collected on that day will not be considered in the derivations.

Once the above rules are applied, the following parameters will be derived (except for WASO which is collected directly from the questionnaire) and used for analysis:

> WASO = Wake After Sleep Onset = Time awake after initial sleep onset but before the final awakening
>
> [redacted]

#3 The team noted some typo in PROMIS conversion table (raw-score to t-score) in the section 15.8 of SAP for LPS16677 – Morpheo study.

Please see corrections below:

- Raw-score = 9 => t-score = 35.2
- Raw-score = 37 => t-score = 73.4
- Raw-score = 40 => t-score = 80.1

#4 In section 8.1.4, it is indicated that SCS rescue medications will be identified using CDGsn00010. The medical team discussed this point, and finally decided to use ATC code to identify SCS from rescue medication page (Asthma Reliever page) to keep consistency with section 15.10 (ie, CDGsn00010 will finally not be used).

#5 Asthma Control Questionnaire ([redacted] and ACQ-5) in section 15.3:

In the final approved SAP, it is indicated that if only one question has missing score, it will be interpolated following the example below:

> (Sum of score at Visit 4/sum of scores excluding question 5 at Visit 3) × score of question 5 at Visit 3.

This will be done, except in rare cases where the sum of scores excluding the missing question at the previous visit is 0. In that case, the missing question will not be imputed at the current visit.

#6 The final SAP approved in February 2022 was developed based on Amended Protocol 1, Version 1.0 dated September 17th, 2020. Contents of final approved SAP Section 13 reflects the changes performed in SAP compared to this amended protocol 1. After the SAP has been signed, a new protocol amendment

was performed (Amended Protocol 2, Version 2.0, dated September 26th 2022). All the changes mentioned in Section 13 from SAP have been implemented in this amended protocol v2.0.

#7 [redacted] If multiple records are available for a same participant at the same date, the earliest record (based on recorded time) will be used for the analysis.

#8 No further analyses are planned for patients recruited by Metasite (Science37) mentioned in protocol amendment v2.0.

#9 The following modifications of prohibited medications identification rules (Section 15.10) will be implemented based on medical team review:

1. Any medication that started after the EOT visit is not prohibited except for the Live (attenuated) vaccines that are prohibited until the EOS visit.
2. Blinded medical review will be conducted in order to confirm (or not) prohibited status for those medications identified as prohibited using programming rules. Only the medications confirmed as prohibited during the medical review will be presented in the analysis.

In those tables (both prior and concomitant prohibited medications), “Medication type" is determined as per CDG (ie, 1 CDG = 1 “Medication type”).

#10 The following modifications of AESI identification rules will be implemented

1. Anaphylactic reactions: includes anaphylactic reaction using CMQ name CMQsn00021 and programmatic identification of cases based on occurrence of at least two events meeting the algorithm criteria occurring within 2 consecutive days of each other. The latter cases identified using the algorithm will undergo blinded medical review taking into account the timing of events relative to each other and to IMP administration for final determination of an anaphylactic reaction or not.
2. Systemic hypersensitivity reactions: CMQ name CMQsn00214 and [AE corrective treatment/therapy=’Y’ or Action taken with IMP=’Drug withdrawn’ or Action taken with IMP=’Drug interrupted’] followed by blinded medical review (documented process) for selection of relevant systemic hypersensitivity events
3. Any severe type of conjunctivitis or blepharitis: Based on the CMQ names CMQ10498 and CMQ10497 with “Severe” ticked in Adverse Events eCRF page.
4. Helminthic infections: Based on CMQ name CMQ10548.
5. Keratitis: Based on CMQ name CMQ10642.
6. Clinically symptomatic eosinophilia: based on CMQ name CMQ10641 followed by blinded medical review (documented process) for selection of relevant eosinophilia events.
7. ALT increase: based on the CMQ names CMQ00029 with the addition of “Is the event an AESI” answered YES on AE eCRF as reported by the investigator.

For AESI Anaphylactic reactions, Clinically symptomatic eosinophilia and Systemic hypersensitivity reactions: blinded medical review will be conducted in order to confirm (or not) AESI status for those AEs identified as AESI using programming rules. Only the AEs confirmed as AESI during the medical review will be presented in the analysis.

#11 The codelist to identify Atopic comorbidities is updated, CMQs CMQ10440, CMQ10539 and CMQ10538 have been replaced by CMQ10799 and CMQ10800 to get more appropriate terms.

#12 In accordance with the general changes made to all Dupi studies, the following changes are made:

1. TEAE period is defined as the time from the first administration of the IMP to the last administration of the IMP + 98 days (instead of 84 days in Section 9 from approved SAP);
2. Concomitant medication is defined as any treatments received concomitantly to the IMP, starting from the date of first IMP administration to the date of last administration + 98 days (instead of 14 days in Section 7.1.2 from approved SAP).

#13 As stratification factors are generally used separately in modeling, both Region (Eastern Europe, rest of world [ROW]) and baseline ICS Dose (high, medium) variables will be included separately in all MMRM models to replace the single variable of stratum (Eastern Europe with high ICS dose, Eastern Europe with medium ICS dose, ROW with high ICS dose and ROW with medium ICS dose).

#14 As only 1 participant has been recruited in [redacted], inclusion in [redacted] (YES/NO) is removed from the covariate list in all analytic models. Also, [redacted] data will be presented as listings instead of being summarized through descriptive statistics.

#15 Section 8.2, qualitative descriptive analysis by visits showing number/proportion of participants in each category will be displayed for [redacted] ("Poor", "Fair", "Good", "Very good", "Excellent"), [redacted] ("very much better", "moderately better", "a little better", "no change", "a little worse", "moderately worse", "very much worse") and [redacted] (adequately controlled [score <= 1.0], inadequately controlled [score > 1]).

#16 Section 15.8, under Asthma Control Questionnaire ([redacted] and ACQ-5), MCID is not an appropriate wording, thus the following clarifications revisions are made.

- "On the 7-point scale of the [redacted], a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer" is replaced by "On the 7-point scale of the [redacted] a change or difference in score of 0.5 represents the within-patient change that can be considered clinically meaningful".
- "On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the MCID" is replaced by "On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 represents the within-patient change threshold that can be considered clinically meaningful.

#17 Section 8.1.4 Subgroup Analysis, listed subgroups may be combined due to small sample size or modified based on actual data collected. For instance, number of severe asthma exacerbation events (1, 2, >2) within 1 year prior to the study will be combined into 2 subgroups (1, >=2) instead of the proposed 3 subgroups; number of controller medications at study entry will be modified from (2, 3) to (2, >=3) to include participants who used more than 3 controllers.

#18 For the Participant [redacted] recruited in [redacted], stratification factors entered into the IVRS system (Region = "All" / ICS dose = "All") do not match with expectations and do not enable to include the participant in the analyses as appropriate. In order to fix this issue and include this participant in the analyses, new specific variables will be derived for Region and ICS dose:

- For the participant [redacted]: Based on external file provided by sponsor (in which Region and ICS dose level are determined according to information recorded in the database)
- For all other participants: Based on values recorded in IVRS.

#19 Section 5.2 Protocol deviations. The following modification will be made: Category "potentially impacting efficacy" removed and category "Impact due to war in Ukraine" added.

The paragraph "All critical or major protocol deviations potentially impacting efficacy analyses (including randomization and drug-dispensing irregularities; see Table 5-1 Randomization and drug dispensing irregularities), and other major or critical deviations will be summarized overall and according to COVID-19 impact (i.e., deviations related to COVID-19 pandemic) for the ITT analysis set by study intervention group and overall using number and percentage." is replaced by "All critical or major protocol deviations (including randomization and drug-dispensing irregularities; see Table 5-1 Randomization and drug dispensing irregularities) will be summarized overall and according to COVID-19 impact (i.e., deviations related to COVID-19 pandemic) as well as impact due to war in Ukraine for the ITT analysis set by study intervention group and overall using number and percentage."

#20 Section 7.2.1 Extent of exposure. As definition for duration of exposure is taking into account last IMP + 14 days, the analysis by categories will be modified to capture appropriately the participants that took their treatment up to the end. The category "> 12 weeks" will be replaced by ">12 and <=14 weeks" and ">14 weeks" (and in cumulative analysis, category ">14 weeks" will be added)

#21 Section 5.1 Disposition. In the approved SAP, it is written: "A summary table to show participant disposition by visit according to trial impact (disruption) due to COVID-19 (visit not done, visit partially done on site, visit partially done by phone and visit done but delayed) will be provided overall and by country for the ITT analysis set".

To avoid confusion with participants included in the subgroup [trial impact (disruption) due to COVID-19], it should be replaced as follows: "A summary table to reflect COVID-19 impact at each visit (visit not done, visit partially done on site, visit partially done by phone and visit done but delayed) will be provided overall and by country for the ITT analysis set". And title of the corresponding table updated accordingly.

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Approve & eSign	[redacted]
Approve & eSign	[redacted]
Approve & eSign	[redacted]

16.1.9.2 Other supporting statistical documentation

Not applicable since LPS16677 statistical documentation consists of SAP only.