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Sanofi SAG

Dupilumab (SAR231893) - LPS15834

Randomized, double blind, placebo controlled study to evaluate the effect of dupilumab on airway inflammation through assessments of lung function, mucus plugging and other lung imaging parameters in patients with asthma

25JUL2023

FINAL STATISTICAL ANALYSIS PLAN

Version 2.0

Prepared by:

Confidential

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LIST OF ABBREVIATIONS

[s]iVaw	Specific airway volume
[s]iRaw	Specific airway resistance
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AQLQ(S)	Asthma Quality of Life Questionnaire with Standardized Activities
AR(1)	First-Order Autoregressive
RNA	Ribonucleic Acid
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
BCP	Business Continuity Plan
BD	Bronchodilator
BMI	Body Mass Index
CI	Confidence Interval
CFD	Computational Fluid Dynamics
CMH	Cochran-Mantel-Haenszel
CS	Compound Symmetry
CSR	Clinical Study Report
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EE	Eastern Europe
ERS	European Respiratory Society
FEF25-75%	Forced Expiratory Flow at 25 and 75% of the Pulmonary Volume
FeNO	Fractional exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FOT	Forced Oscillation Technique
FRC	Functional Residual Capacity
FRI	Functional Respiratory Imaging
FVC	Forced Vital Capacity
GLMM	Generalized Linear Mixed Model
HBcAb	Hepatitis B core Antibody

HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HCVAb	Hepatitis C Virus Antibodies
HIV	Human Immunodeficiency Virus
HLT	High Level Term
HLGT	High Level Group Term
HR	Heart Rate
HRCT	High-Resolution Computed Tomography
IAD	Internal Airflow Distribution
IcEv	Intercurrent Event
ICS	Inhaled Corticosteroids
IgM	Immunoglobulines M
IMP	Investigational Medicinal Product
ITT	Intent-To-Treat
iV/Q	Image-based ventilation/perfusion
iVaww	Airway wall volume
iVlobes	Lobar volumes
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-Acting Beta-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LLT	Lowest Level Term
LTRA	Leukotriene Receptor Antagonists
LS	Least Square
MAR	Missing At Random
MCID	Minimal Clinically Important Difference
MCMC	Markov Chain Monte Carlo
MDCT	Multi-detector Computed Tomography
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
NIMP	Non-Investigational Medicinal Product
PCSA	Potentially Clinically Significant Abnormalities
ppb	Parts Per Billion
PRO	Patient-Reported Outcomes

PT	Preferred Term
Q1	First Quartile
Q2W	Every 2 Weeks
Q3	Third Quartile
QoL	Quality of Life
ROW	Rest of World
SABA	Short-Acting Beta Agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TLC	Total Lung Capacity
TLFs	Tables, Listings, Figures
TOEP	Homogeneous Toeplitz
TOEPH	Heterogeneous Toeplitz
UCSF	University of California, San Francisco
ULN	Upper Limit of Normal
UN	Unstructured
US	United States
WHO-DD	World Health Organization-Drug Dictionary

DOCUMENT HISTORY-CHANGES COMPARED TO PREVIOUS VERSION OF SAP

Version	Date	Changes
Draft 1.0	04OCT2021	Initiation
Draft 2.0	25FEB2022	Updates following Sanofi's comments - Updated MMRM model for [s]iVaw - Removed supplementary analysis - Updated model for FRI secondary endpoints
Draft 3.0	11JUL2023	- Updated model for FeNO <25 ppb achievement and moved to primary endpoint - Pre-BD FEV_1 has been downgraded from primary to secondary endpoint - Post-BD FEV_1 is still a secondary endpoint but will be removed from hierarchical testing order - Mucus score was upgraded from tertiary to secondary endpoint - Added tertiary endpoints change from baseline in PI10, Airway Wall Area, Wall Area Percentage, Airway Radius, Mucus volume, Reactance Area, pre- and post-BD FEV_1/FVC, pre- and post-BD FEF25-75% - Added composite endpoints - Added supplementary analyses - Updated baseline and reference day definitions - Added deviations related to Ukrainian crisis
Final 1.0	20JUL2023	- Changed criteria on supplementary analyses - Added supplementary analysis removing data with technical issues
Final 2.0	25JUL2023	- Added tertiary endpoints change from baseline in airway resistance R5 and R20 measured by forced oscillometry

1. INTRODUCTION

This document provides the detailed statistical methodology for the analysis of data from the Sanofi Group study LPS15834. 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 Clinical Trial protocol, Version 3.0, dated on 13th April 2023. 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 lung inflammation and related changes in airway volumes detectable by functional respiratory imaging.	• Proportion of participants achieving fractional exhaled nitric oxide (FeNO) <25 parts per billion (ppb) at Week 24 • Percent change from baseline to Week 24 in untrimmed distal specific airway volume ([s]iVaw) at total lung capacity (TLC)
Secondary	
• To evaluate the effect of dupilumab at Week 24 on bronchodynamics, hyperinflation, airway resistance, airway wall volume, ventilation defects and mucus plugging derived from high-resolution computed tomography (HRCT) scans, patient-reported outcomes (PRO), FeNO and spirometry.	• Percent change from baseline to Week 24 in untrimmed distal specific airway volume ([s]iVaw) at functional residual capacity (FRC) • Percent change from baseline to Week 24 in trimmed distal specific airway resistance ([s]iRaw) at TLC • Percent change from baseline to Week 24 in trimmed distal specific airway resistance ([s]iRaw) at FRC • Percent change from baseline to Week 24 in global lung lobar volumes (iVlobes) at TLC • Change from baseline to Week 24 in HRCT-based internal airflow distribution (IAD) for each lung zone • Change from baseline to Week 24 in image-based ventilation/perfusion (iV/Q) at TLC for each lung zone • Change from baseline to Week 24 in global lung mucus score (UCSF mucus scoring) • Change from baseline to Week 24 in FeNO • Change from baseline to Week 24 in pre-bronchodilator FEV_1 • Change from baseline to Week 24 in post-bronchodilator FEV_1 • Change from baseline to Week 24 in 7 item Asthma Control Questionnaire (ACQ-7)
• To evaluate safety of dupilumab	• Incidence of treatment emergent adverse events (TEAE) and serious adverse events (SAE) including clinically significant changes in vital signs and laboratory abnormalities • Incidence of adverse events of special interest (AESI)

Objectives	Endpoints
[redacted]	

Objectives	Endpoints
[redacted]	

Table 2-2 Summary of primary estimands for main objectives

Endpoint Category (estimand)	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To assess the effect of dupilumab on lung inflammation and related changes in airway volumes detectable by functional respiratory imaging.				
Primary endpoints	Proportion of participants achieving FeNO <25 ppb at Week 24	ITT	• Discontinuation of study intervention due to Covid-19 pandemic[a] (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).	Achievement of FeNO <25 ppb at Week 24 will be analyzed using a Cochran-Mantal-Haenszel (CMH) test adjusted by stratification factors (region and ICS dose level). Corresponding odds ratios and 95% CI with p-value will be reported. Missing data at Week 24 will be considered as non-responders.
	Percent change from baseline to Week 24 in untrimmed distal specific airway volume ([s]iVaw) at total lung capacity (TLC)	ITT	• Discontinuation of study intervention due to Covid-19 pandemic[a] (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) framework will be used. The MMRM will use percent change from baseline in untrimmed distal [s]iVaw at TLC up to Week 24 as the response variable, and will include study intervention, baseline value, region, ICS dose level, visits, study intervention by visit interaction, and baseline by visit interaction terms all as fixed effects. Region, ICS, study intervention and visits will be considered as categorical parameters. No explicit imputation will be done for missing data. Baseline values corresponding to the outcome variables should be used.
Secondary objective: To evaluate the effect of dupilumab at Week 24 on bronchodynamics, hyperinflation, airway resistance, airway wall volume, ventilation defects and mucus plugging derived from high-resolution computed tomography (HRCT) scans, patient-reported outcomes, FeNO and spirometry.				

Endpoint Category (estimand)	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary endpoint	Change or percent change from baseline in respiratory related outcomes	ITT	• Discontinuation of study intervention due to Covid-19 pandemic[a] (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).	For spirometry and biomarker parameters, a mixed effect model for repeated measures (MMRM) under the missing at random (MAR) framework based on change from baseline up to Week 24 will be used. The MMRM will include study intervention, baseline value, region, Inhaled Corticosteroids (ICS) dose level, visits, age, height, gender, study intervention by visit interaction, and baseline by visit interaction terms all as fixed effects. Region, ICS, gender, study intervention and visits will be considered as categorical parameters. No explicit imputation will be done for missing data. Baseline values corresponding to the outcome variables should be used. For Functional Respiratory (FRI) parameters, the same MMRM model as for untrimmed distal [s]iVaw at TLC primary endpoint will be used. Baseline values corresponding to the outcome variables should be used. For Asthma Control Questionnaire (ACQ-7), a mixed effect model for repeated measures (MMRM) under the missing at random (MAR) framework based on change from baseline up to Week 24 will be used. The MMRM will include study intervention, baseline value, region, Inhaled Corticosteroids (ICS) dose level, visits, study intervention by visit interaction, and baseline by visit interaction terms all as fixed effects

a 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, 2:1 randomized, parallel, multinational, multicenter study, with a 24-week double-blind placebo-controlled treatment period to assess the effect of dupilumab on airway inflammation through assessments of lung function, mucus plugging, and other lung imaging parameters in participants with asthma.

Approximately 97 participants will be randomly assigned to study intervention, in a 2:1 dupilumab to placebo ratio, such that approximately 87 evaluable participants complete the study, assuming a 10% dropout rate (approximately 58 in the active group and 29 in the placebo group). Randomization will be stratified by dose level (medium/high – no less than 40% in 'high ICS' stratum) of inhaled corticosteroids (ICS) and region (Eastern Europe (EE)/Rest of the World (ROW)). In total, no more than 40% participants should be in EE strata.

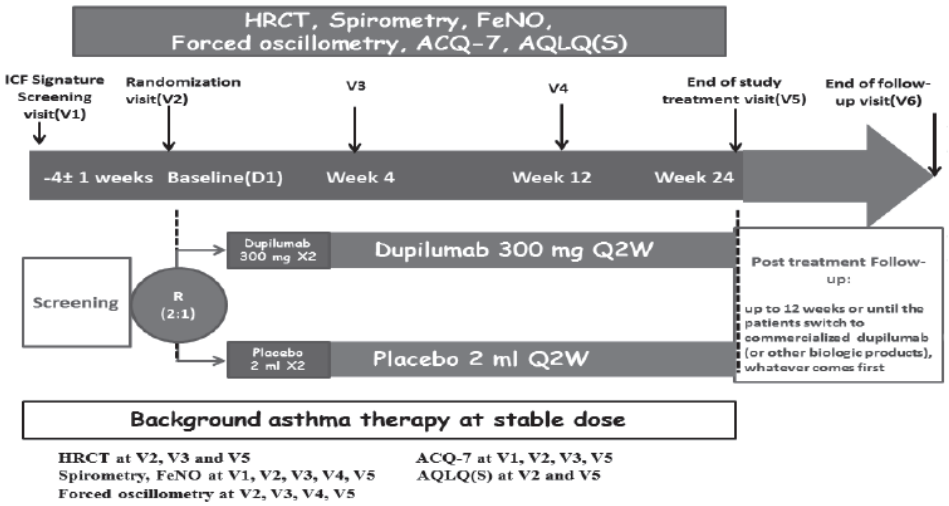
The study will comprise of:

- Screening period: 4 weeks (±1 week), from signed informed consent to randomization (Day [-35, -21] to Day -1).
- Randomized, placebo-controlled treatment period: 24 weeks from baseline (Day 1).
- Post-treatment follow-up period: up to 12 weeks or until the participant switches to commercialized dupilumab (or other biologic product), whichever comes first.

Study duration for each participant will be a total of minimum 29 weeks and up to 41 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 (V6).

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

Figure 3-1 Study plan



ACQ-7= 7-item Asthma Control Questionnaire; AQLQ(S) =Asthma Quality of Life Questionnaire with Standardized Activities; D=Day; FeNO= Fractional exhaled nitric oxide; FU= Follow-up; HRCT= High-resolution computed tomography; ICF=Informed Consent Form; mg=milligram; ml=milliliter; Q2W= every 2 weeks; R=Randomization; V=Visit

3.2. Study endpoints

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

3.3. Study interventions

The highest approved dose regimen of SC dupilumab has been selected for this study (300 mg Q2W).

Participants will receive;

- Dupilumab 600 mg (2 x 300 mg dupilumab subcutaneous injections) on Day 1 (ie, the loading dose), followed by 1 dupilumab injection of 300 mg every two weeks (Q2W) until Week 24.
- Matching placebo for dupilumab (2 x 2 mL placebo subcutaneous injections) on Day 1 (loading dose), then 1 placebo injection Q2W until Week 24.

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) in combination with a second controller (ie, Long-Acting Beta-Agonists (LABA), Leukotriene Receptor Antagonists (LTRA), theophylline). A third controller is allowed but not mandatory. The dose regimen should be stable for ≥1 month before V1, during the screening and treatment period. Short-acting β2 agonists may be used as rescue medication during the study if needed.

In case of severe 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

In order to preserve the type I error at 0.05 level for the two primary endpoints, a hierarchical testing procedure will be applied at a 2-sided 5% significance level. The hierarchy of the tests for primary endpoints will be:

1. Proportion of participants achieving response of FeNO <25 ppb at Week 24
2. Percentage change from baseline to Week 24 in untrimmed distal [s]iVaw at TLC

After the significance has been achieved for 2 primary endpoints, the other selected secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significance level. The whole list of secondary endpoints to be tested in the hierarchical order will be specified in Section 8.2.5.

[redacted]

4.2. Randomization, stratification, and blinding

Randomization will be stratified by ICS dose level (medium/high- no less than 40% in 'high ICS' stratum) and region (EE/ROW - no more than 40% participants in EE stratum).

A randomized participant is defined as a participant who is registered and assigned with a study intervention kit number from the centralized treatment allocation system regardless of whether the intervention kit was used, as documented from its log file. A participant cannot be randomized more than once in the study.

4.3. Analysis set

Participants exposed to Investigational Medicinal Product (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 (CSR).

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/Interactive Web Response System (IVRS/IWRS).

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 Intent-to-Treat (ITT) analysis set consists of randomized participant (participant with a study intervention kit number allocated and recorded in the IVRS/IWRS 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.

4.3.3. Safety set

The Safety set includes all randomized participants who received at least 1 injection of IMP. Participants will be analyzed according to the study intervention they actually received. Randomized participants for whom it is unclear whether the study medication was taken will be included in the safety set as randomized. For participants receiving more than one IMP during the study (ie, 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 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 300 mg q2w	Dupilumab 300 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.

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 (CI) 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'. If a p-value is greater than 0.999 it will be reported as '>0.999'.

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 efficacy parameters, the baseline value is defined as the last available valid (non-missing) value up to and including the date 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.

For safety parameters, the baseline value is defined as the last available valid (non-missing) value up to and including the date of first dose of IMP.

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 baseline 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:

$$\text{WEEKS} = \text{DAYS} / 7$$

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

$$\text{MONTHS} = \text{DAYS} / 30.4375$$

4.4.7. Change from baseline and percent change from baseline

Change from baseline is defined as:

$$\text{Change from baseline} = \text{Value at specific time point} - \text{Baseline value}$$

Percent change from baseline is defined as:

$$\text{Percent change from baseline}(\%) = \frac{\text{Value at specific timepoint} - \text{Baseline value}}{\text{Baseline value}} \times 100\%$$

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 24
IcEv2 (discontinuation of study intervention not due to Covid-19)	Premature study intervention discontinuation not due to Covid-19 pandemic before Week 24

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 study intervention period
- Participants who discontinued the study intervention 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 discontinued 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 24
- Participants who discontinued the study after Week 24 (ie, during post-study intervention follow-up period)
- Participants who had rescue medications during the study intervention period:
  - Participants who have completed the study intervention period and had rescue medications
  - Participants who did not complete the study intervention 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.

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

Participants with permanent study intervention and study discontinuation (early withdrawals) will be identified and described in separate listings (with the reason of discontinuation and the specification in case of other reason).

Additionally, trial impact (disruption) due to COVID-19 will be summarized for the ITT analysis set by study intervention group and overall using number and percentage. Participants for whom at least one of the following events occur during the study will be presented:

- 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 deviation due to COVID-19 pandemic

Some safety (adverse events) analyses will also be repeated on the subgroup 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 pandemic (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. Deviations related to Ukrainian crisis will be assessed as “Exceptional situation”.

A listing of participants with at least one critical or major protocol deviations 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 CSR. 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 study intervention 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

The following demographics and participant characteristics will be summarized by treatment group and overall:

- Age (years)
- Age categories (≥18 to <40, ≥40 to <70, ≥70)
- 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, Multiple, Not Reported, Unknown)
- Baseline body weight (kg)
- Baseline body weight categories (<70, ≥70 to <100, ≥100)
- Baseline height (cm)
- Baseline body mass index (BMI) (kg/m²) derived as: (Weight in kg)/(Height in meters)²
- Baseline BMI categories (<15, ≥15 to <25, ≥25 to <30, ≥30)
- Region (EE/ROW)

6.2. Baseline disease characteristics

The following baseline disease characteristics will be summarized by study intervention group and overall:

6.2.1. Respiratory characteristics at baseline

- Spirometry (see Section 15.9):
  - Pre-BD FEV_1 (L)
  - Post-BD FEV_1 (L)
  - % predicted pre-BD FEV_1 (%)
  - % predicted post-BD FEV_1 (%)
  - Pre-BD FVC (L)
  - Post-BD FVC (L)
  - % predicted Pre-BD FVC (%)
  - % predicted Post-BD FVC (%)
  - Pre-BD FEV_1/FVC
  - Post-BD FEV_1/FVC

  - Pre-BD FEF 25-75% (L/s)
  - Post-BD FEF 25-75% (L/s)
- The following Functional Respiratory Imaging (FRI) parameters (see Section 15.10), based on low-dose inspiratory-expiratory multi-slice computed tomography images and computational fluid dynamics flow simulations will be presented:
  - Untrimmed distal airway volume ([s]iVaw) (in mL) at total lung capacity (TLC)
  - Untrimmed distal [s]iVaw (in mL) at functional residual capacity (FRC)
  - Trimmed distal airway resistance ([s]iRaw) (in KPA*S/L) at TLC
  - Trimmed distal [s]iRaw (in KPA*S/L) at FRC
  - UCSF mucus score, global and for each lung zone (RUL, RML, RLL, LUL, LLL)
  - Untrimmed distal airway wall volume (iVaww) (in mL) at TLC
  - Global lung lobar volumes (iVlobes) (in L) at TLC
  - Global lung iVlobes (in L) at FRC
  - Ventilation/perfusion ratio (iV/Q) at TLC for each lung zone (RUL, RML, RUL+RML, RLL, LUL, LLL)
  - Blood vessel density at TLC (mL) (overall lung)
  - HRCT based Internal lobar airflow distribution (IAD) (%) for each lung zone (RUL, RML, RUL+RML, RLL, LUL, LLL)
  - HRCT based airway occlusions at FRC (in %) for each lung zone (RUL, RML, RUL+RML, RLL, LUL, LLL)
  - Mucus volume (mL), global and for each lung zone (RUL, RML, RLL, LUL, LLL)
  - PI10 (mm)
  - Airway wall area (mm^2)
  - Wall area percentage (%)
  - Airway radius (mm)
- Forced oscillometry (see Section 15.11):
  - Airway resistance from R5 to R20 (in KPA*S/L)
  - Reactance area (kPa/L)
  - Airway resistance R5 (in KPA*S/L)
  - Airway resistance R20 (in KPA*S/L)

Notes for FRI parameters:

For each parameter, the zone to be presented and whether trimmed or untrimmed data should be presented are listed in the list of parameters above.

All FRI parameters are assessed in the following different zones of the respiratory system:

- Overall lung (except for HRCT based IAD)
- Right upper lobe (RUL)
- Right middle lobe (RML)
- Right lower lobe (RLL)
- Left upper lobe (LUL)
- Left lower lobe (LLL)

[s]iVaw, [s]iRaw and iVaww are also assessed in the following zones of the respiratory system:

- Distal lung

However, the possibility exists that for some participants no distinction can be made between the different lung lobes. In this case, the following zones can also be identified, but will be excluded from tables, figures and models (only listed):

- Right upper and middle lobe (RUL+RML)
- Right middle and lower lobe (RML+RLL)
- Right upper and lower lobe (RUL+RLL)
- Right upper, middle and lower lobe (RUL+RML+RLL)
- Left upper and lower lobe (LUL+LLL)

Trimmed and untrimmed results (see Section 15.10) are available for [s]iVaw, [s]iRaw and iVaww.

6.2.2. Asthma questionnaires at baseline

The following asthma questionnaires (see Section 15.8) will be summarized at baseline:

- 7-item Asthma Control Questionnaire (ACQ-7) score
- ACQ-6 score
- ACQ-5 score
- Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ(S)) global score

6.2.3. Asthma and associated disease characteristics at baseline

Asthma history will be summarized by study intervention group and overall:

- Dose level of inhaled corticosteroid (ICS) (Medium, High)
- Age at asthma diagnosis (years),
- Age at asthma diagnosis categories (<18, ≥18 to <40, ≥40 to <70, ≥70),
- 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),
- Time since last severe asthma exacerbation (months),
- Number of controller medications at study entry (2 or 3)
- Atopic comorbid condition (yes/no)

The age at asthma diagnosis is defined as the date of asthma diagnosis minus the year of birth and June 30th divided by 365.25, keeping the integer part of the result.

The time since last severe asthma exacerbation in months is defined as the informed consent date minus the date of the last severe asthma exacerbation divided by 30.4375.

Exacerbation is defined as deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids.

6.2.4. Biomarkers at baseline

The following biomarkers (see Section 15.12) will be summarized at baseline:

- FeNO (ppb)
- FeNO in class (<25, ≥25 to <50, >=50 ppb)
- Blood Eosinophil count (cells/µL)
- Eosinophils counts in class (≥300 to <500, ≥500 cells/µL)

Blood Eosinophils counts collected in 10^9/L will be converted to cells/µL using the following formula:

1 10^9/L *1000 = cells/µL

6.3. Tobacco usage

The following smoking habits at screening will be summarized by study intervention group and overall:

- Tobacco consumption: status (never, current, former) and amount (cigarette) per day
- Electronic cigarette consumption: status (never, current, former) and amount (mg) per day

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. SOC will be sorted by internationally agreed order of primary SOC, and HLT and PT will be sorted by alphabetical order. Participants experiencing severe 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 set. Atopic comorbidities will be identified via a file provided by Sanofi containing the following CMQ codes: CMQ10646, CMQ10540, CMQ10541, CMQ10537, CMQ10076, CMQ10799, CMQ10800.

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.

6.6. Other background information

Not applicable.

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.

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.

A given medication can be classified as a prior medication as well as a concomitant medication.

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, Long-Acting Muscarinic Antagonist (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 (Short-Acting Beta Agonists (SABA), systemic corticosteroids, other) and standardized medication name (see Section 15.13).
  Note: These medications are recorded in the Asthma reliever medication eCRF page.

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

The prior prohibited medications will also be presented by prohibited medication category as defined in deviation and standardized medication name (see Section 15.13).

7.1.2. Concomitant medications

Concomitant medications are any treatments received by the participant concomitantly to the IMP, starting from the 1st administration of IMP to the date of last administration +98 days.

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 15.13).
  Note: These medications are recorded in the asthma reliever medication eCRF page.
- Other concomitant medications.
  Note: These medications are recorded in the other medications eCRF page.

The concomitant prohibited medications will also be presented by prohibited medication category as defined in deviation and standardized medication name (see Section 15.9).

7.1.3. Post-treatment medications

Post-treatment medications are those the participant took (continued or initiated) in the period running from the 99th day after the last administration of IMP up to the end of the study. Post-treatment medications will not be summarized or presented in the CSR.

7.2. Study interventions

The extent of IMP exposure and compliance will be assessed and summarized by actual study intervention group for the safety 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 administration dose date – first IMP administration dose 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 and ≤16 weeks
- >16 and ≤20 weeks
- >20 and ≤24 weeks
- >24 and ≤26 weeks
- >26 weeks

and cumulatively according to the following categories:

- ≥1 day
- >2 weeks
- >4 weeks
- >8 weeks
- >12 weeks
- >16 weeks
- >20 weeks
- >24 weeks
- >26 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:

- <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 during an interval of less than 11 days. 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

Efficacy analyses will be performed on the ITT analysis set.

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

For all efficacy analyses, time window will be used to assign the visit (see Section 15.5).

For the analysis of primary objective in the study intervention period,

- The null statistical hypothesis tested is that 1) the proportion of participants achieving response of FeNO <25 ppb at Week 24 is the same between dupilumab and placebo group; 2) the percentage change from baseline in untrimmed distal [s]iVaw is the same between dupilumab and placebo group.
- The alternative statistical hypothesis tested is that 1) the proportion of participants achieving response of FeNO <25 ppb at Week 24 is different between dupilumab and placebo group; 2) the percentage change from baseline in untrimmed distal [s]iVaw is different between dupilumab and placebo group.

In order to preserve the type I error at 0.05 level for the two primary endpoints, a hierarchical testing procedure will be adopted. The tests will be performed in this order:

1. Proportion of participants achieving response of FeNO <25 ppb at Week 24
2. Percentage change from baseline to Week 24 in untrimmed distal [s]iVaw at TLC

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. Refer to Table 2-2 for more details.

For efficacy endpoints where a change from baseline or percent change from baseline is assessed, only the participants with a baseline and at least one post-baseline value available will be included in the analysis model (number of participants included in the analysis model reported in the table). All available results will be included in the descriptive statistics.

Line plots for change and percent 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.

Bar plots for percentage of participants having achieved FeNO <25 parts per billion (ppb) at Week 24 will be presented by study intervention group, displaying the percentage of achievers participants at each visit.

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 24 only.

8.1. Primary efficacy endpoint

The two primary endpoints are:

- Proportion of participants achieving response of FeNO <25 ppb at Week 24
- Percent change from baseline to week 24 in untrimmed distal specific airway volume ([s]iVaw) at total lung capacity (TLC) (see Section 15.10)

8.1.1. Primary analysis

Proportion of participants achieving FeNO <25 ppb at week 24 will be analyzed with a Cochran-Mantel-Haenszel (CMH) test adjusted by stratification factors (ICS dose level at baseline and region). Comparison of the proportions of responders between dupilumab and placebo will be derived, and corresponding odds ratios and 95% CI along with the p-value will be reported.

For participants who discontinued the study treatment not due to COVID-19 pandemic, off-treatment data will be used to determine the responder/non-responder status. For any participants who discontinued the study treatment due to COVID-19 pandemic, off-treatment data will be set to missing. Missing data at week 24 will be considered as non-responders.

Percent change from baseline in untrimmed distal [s]iVaw at TLC will be analyzed with a MMRM model under the MAR framework. The MMRM model will use percent change from baseline in untrimmed distal [s]iVaw up to week 24 as response variable and include study intervention (dupilumab, placebo), baseline value of untrimmed distal [s]iVaw at TLC, region (EE/ROW), ICS dose level (medium/high), visits (up to week 24), study intervention by visit interaction, and baseline untrimmed distal [s]iVaw at TLC by visit interaction terms all as fixed effects. An unstructured correlation matrix will be used to model the within-participant errors.

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 LS mean in percent 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 at all scheduled visits. The p-value corresponding to the LS mean difference will be provided at Week 24 only.

For participants who discontinued the study intervention before Week 24 not due to the COVID-19 pandemic, off-study intervention imaging data measured up to Week 24 will be included in the analysis. In contrast, for any participants discontinuing the study intervention due to the COVID-19 pandemic, off-study intervention data will not be included (ie, set to missing) but will be assumed missing at random.

Note: baseline value corresponds to the baseline value of the variable being analyzed. In case of variables in the percentage scale, this will be the baseline value on the raw scale.

Data may be logarithmically transformed prior to analysis if extreme skewness was observed based on blinded data review.

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, Table 2-1).

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 kg)
- Baseline BMI (<25, ≥25 to <30, ≥30)
- Region (EE/ROW)
- Baseline ICS dose level (Medium, High)
- Age of asthma diagnosis (<18, ≥18 to <40, ≥40 years)
- Number of severe asthma exacerbation events within 1 year prior to the study (1, >1)
- Number of controller medications at study entry (2, 3)
- Smoking history (Former, Never)
- Baseline FeNO (≥25 to <50, >=50 ppb)
- Baseline Eosinophils (<500, ≥500 cells/µL)
- Baseline ACQ-5
  - (≤3, >3)
  - (≤3.5, >3.5)
- Baseline Global Lung Mucus Score
  - Low (0-3.5)
  - High (4-20)

Subgroups might be combined in case the sample size is too small.

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 two primary endpoints of achievement of FeNO <25 ppb at Week 24 and percent change from baseline to week 24 in untrimmed distal [s]iVaw at TLC will be carried out. For the latter, an analysis of covariance model (ANCOVA) with data from multiple imputation (MI) on missing results under an assumption of missing at random (MAR) will be used. For response of FeNO <25 ppb at week 24, a CMH testing procedure with data from multiple imputation (MI) on missing results under an assumption of missing at random (MAR) will be performed. Under this assumption, each missing score will be imputed 100 times and incorporated with non-missing data form 100 complete datasets. Each dataset will include FeNO / untrimmed distal [s]iVaw at baseline, week 4, week 12 (only for FeNO), and week 24, 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 the endpoint, 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 remaining missing value by study intervention group up to week 24. In the imputation regression model, the following covariates will be included:
  - region (EE/ROW) and ICS dose level (medium/high)

  Percent change from baseline at week 24 and achievement of FeNO <25 ppb 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 the following models.
- Repeatedly perform ANCOVA modeling for each of 100 datasets with full imputation for missing values. Percent change from baseline of untrimmed distal [s]iVaw at TLC at week 24 will be analyzed on the ITT population in this ANCOVA model, and study intervention (Dupilumab, Placebo), baseline of the analyzed endpoint and respective above covariates, will be included as covariates.
- The adjusted LS means in change or percent 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 of the differences generated from the 100 ANCOVA models will be combined using Rubin's formula and presented in a statistical table for the ITT population.

- Repeatedly perform CMH testing on each of 100 datasets with full imputation for missing values. Achievement of response of FeNO <25 ppb at week 24 will be analyzed on the ITT population, adjusted on stratification factors.
- The Wilson-Hilferty transformation will be used to perform a combined CMH test and odds-ratios will be combined using a log transformation and Rubin's formula. The combined p-value, odds-ratio and corresponding CIs will be presented in a statistical table for the ITT population.

8.1.6. Supplementary analysis

A supplementary subgroup analysis will be performed on primary endpoints, for the following subgroups:

- Participants who had concomitant SCS rescue medications (identified with file provided by Sanofi containing CDGsn00010 medications) (Yes, No)
- Participants who have respected SABA washout period (only for untrimmed distal [s]iVaw)
- Removing data with technical issues (only for untrimmed distal [s]iVaw)

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

Results will also be illustrated with forest plots.

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 interruption, 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. 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.

Missing data due to Covid-19 pandemic is likely to be missing at random. 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 efficacy endpoints

8.2.1. Lung function measured by spirometry

Pre-BD FEV_1 and Post-BD FEV_1 (see Section 15.9) will be summarized in terms of actual value and change from baseline at baseline and at week 24.

In addition, at each post-baseline visit, the change from baseline will be modelled using an MMRM model under the missing at random framework. The MMRM model will include study intervention (dupilumab, placebo), baseline value of the parameter, region (EE/ROW), ICS dose level (medium/high), visits (up to week 24), age (years), height (cm), gender (male/female), study intervention by visit interaction, and baseline value of the parameter by visit interaction terms all as fixed effects. An unstructured (UN) correlation matrix will be used to model the within-participant errors.

The same strategy as for MMRM model for primary endpoint untrimmed distal [s]iVaw will be used for the selection of the covariance structure if MMRM under unstructured correlation matrix fails to achieve convergence.

8.2.2. Fractional Exhaled Nitric Oxide (FeNO)

FeNO (see Section 15.12) will be summarized in terms of actual value and change from baseline at Week 24).

In addition, at each post-baseline visit, the change from baseline will be modelled using the same MMRM model as the one used for the secondary endpoint relating to pre-BD and post-BD FEV_1. LS mean of each study intervention group, LS mean difference between the dupilumab and placebo groups, and the corresponding SEs and 95% CIs will be provided at all scheduled visits. The p-value corresponding to the LS mean difference will be provided at Week 24 only. FeNO data may be logarithmically transformed prior to analysis if extreme skewness was observed based on blinded data review.

The same strategy as for MMRM model for primary endpoint untrimmed distal [s]iVaw will be used for the selection of the covariance structure if MMRM under unstructured correlation matrix fails to achieve convergence.

8.2.3. Functional Respiratory Imaging (FRI)

FRI secondary endpoints (see Section 15.10) will be summarized in terms of actual value and change from baseline or percent change from baseline to each post-baseline visit (Week 4 and Week 24).

In addition, at each post-baseline visit, the change from baseline or percent change from baseline will be modelled using the same MMRM model as the one used for the primary end point relating to untrimmed distal [s]iVaw at TLC. Baseline value will be the one of the variable being analyzed and, in case of variables in the percentage scale, it will be the baseline value on the raw scale. LS mean of each study intervention group, LS mean difference between the dupilumab and placebo groups, and the corresponding SEs and 95% CIs will be provided at all scheduled visits. The p-value corresponding to the LS mean difference will be provided at Week 24 only.

The same strategy as for MMRM model for primary endpoint untrimmed distal [s]iVaw will be used for the selection of the covariance structure if MMRM under unstructured correlation matrix fails to achieve convergence.

FRI secondary endpoints are the following:

- Untrimmed distal [s]iVaw at FRC (percentage change from baseline)
- Trimmed distal [s]iRaw at TLC (percentage change from baseline)
- Trimmed distal [s]iRaw at FRC (percentage change from baseline)
- Global lung iVlobes at TLC (percentage change from baseline)
- iV/Q at TLC (change from baseline) for lower and upper lung
- HRCT based IAD (change from baseline) for lower and upper lung
- Global lung UCSF mucus scoring (change from baseline)

* Data may be logarithmically transformed prior to analysis if extreme skewness was observed based on blinded data review.

8.2.4. Asthma Control Questionnaire (ACQ-7)

ACQ-7 score (see Section 15.8) will be summarized in terms of actual value and change from baseline at baseline and at each post-baseline visit (Week 4 and Week 24).

In addition, at each post-baseline visit, the change from baseline will be modelled using MMRM model including study intervention (dupilumab, placebo), baseline value of the score, region (EE/ROW), ICS dose level (medium/high), visits (up to Week 24), study intervention by visit interaction, and baseline score by visit interaction terms all as fixed effects. An unstructured correlation matrix will be used to model the within-participant errors. LS mean of each study intervention group, LS mean difference between the dupilumab and placebo groups, and the corresponding SEs and 95% CIs will be provided at all scheduled visits. The p-value corresponding to the LS mean difference will be provided at Week 24 only.

The same strategy as for MMRM model for primary endpoint untrimmed distal [s]iVaw will be used for the selection of the covariance structure if MMRM under unstructured correlation matrix fails to achieve convergence.

8.2.5. Multiplicity issues

The overall type-I error rate will be controlled at the two-sided 0.05 level using a hierarchical testing procedure. The primary endpoints will be tested sequentially in the order described in Section 8. The secondary endpoints will be tested following the hierarchical testing procedure with a pre-specified order, that is, inferential conclusions about successive secondary endpoints require statistical significance at 0.05 significance level of the previous one.

The following secondary endpoints will be included in the multiplicity adjustment scheme and tested in the following order:

- Change from baseline to Week 24 in global lung UCSF Mucus Scoring
- Percent change from baseline to week 24 in trimmed distal [s]iRaw at TLC

Each endpoint will be tested at 0.05 (two-sided) level of significance. If at any step the null statistical hypothesis of no study intervention difference is not rejected, the endpoints listed after that step will be reported at nominal level, otherwise will be technically eligible for being declared significant.

8.2.6. Supplementary analysis

Change from baseline to week 24 in pre-BD FEV_1 will be analyzed as a supplementary analysis in the following ways:

- Removing potential outliers using z-score method

Records with change from baseline value more than 3 standard deviations away from the mean change from baseline for each visit and treatment group will be considered as potential outliers.

Change from baseline will be modelled using an MMRM model under the missing at random framework. The MMRM model will include study intervention (dupilumab, placebo), baseline value of pre-BD FEV_1, region (EE/ROW), ICS dose level (medium/high), visits (up to Week 24), age (years), height (cm), gender (male/female), study intervention by visit interaction, and baseline pre-BD FEV_1 by visit interaction terms all as fixed effects. An unstructured (UN) correlation matrix will be used to model the within-participant errors.

The same strategy as for MMRM model for primary endpoint untrimmed distal [s]iVaw will be used for the selection of the covariance structure if MMRM under unstructured correlation matrix fails to achieve convergence.

- Using data borrowing approach

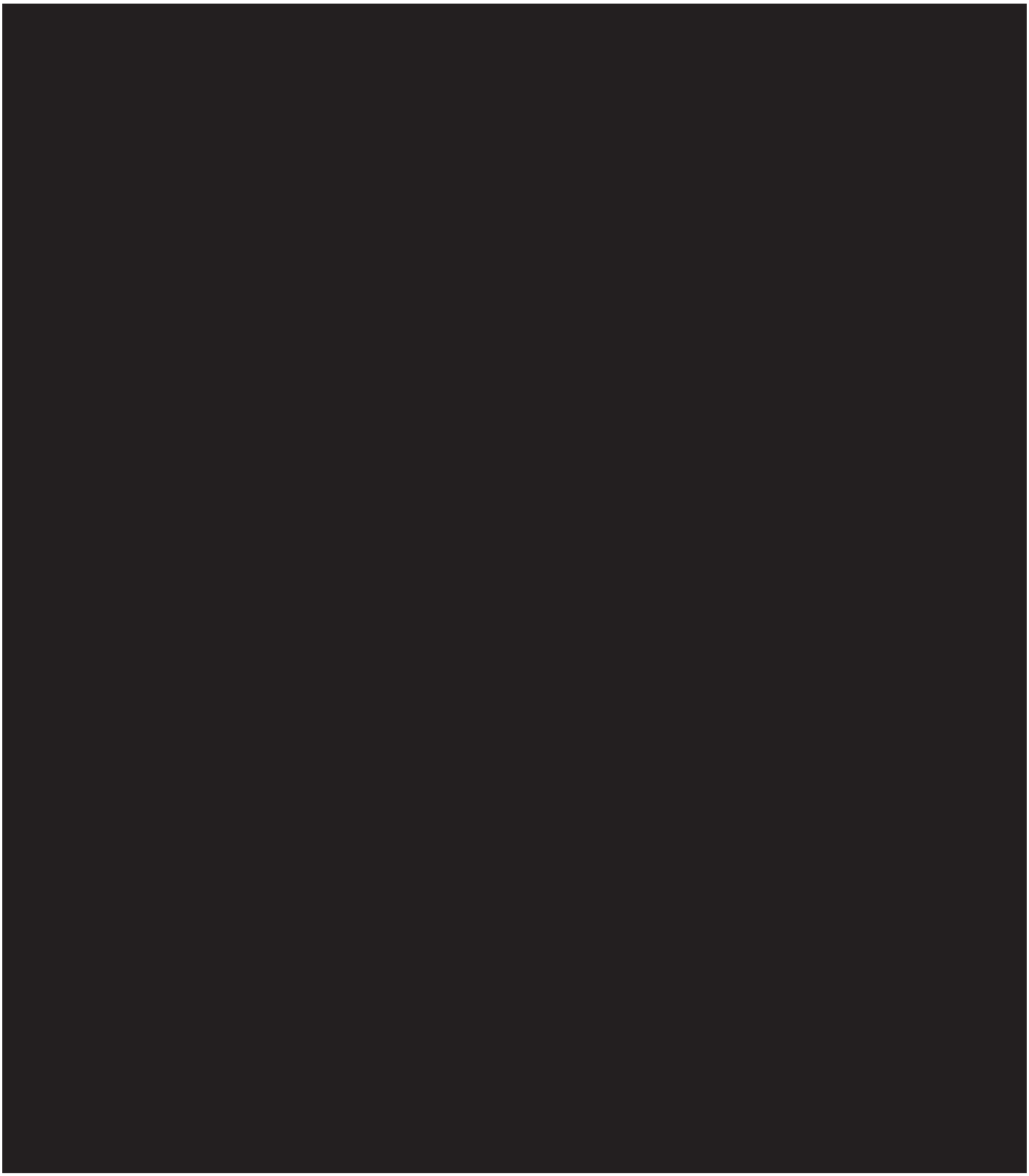
The Dupilumab Phase III 'LIBERTY ASTHMA QUEST' study will be used as the source of historical data, and the propensity score matching method will be implemented first to select appropriate participants, then the Bayesian dynamic borrowing approach will be implemented to evaluate the change from baseline to Week 24 in pre-BD FEV_1. The adjusted LS means in each study intervention group, the LS mean difference between the dupilumab and placebo groups, and the corresponding SE and 95% CI will be provided, and the nominal p-value corresponding to the LS mean difference will be provided for descriptive purpose only.

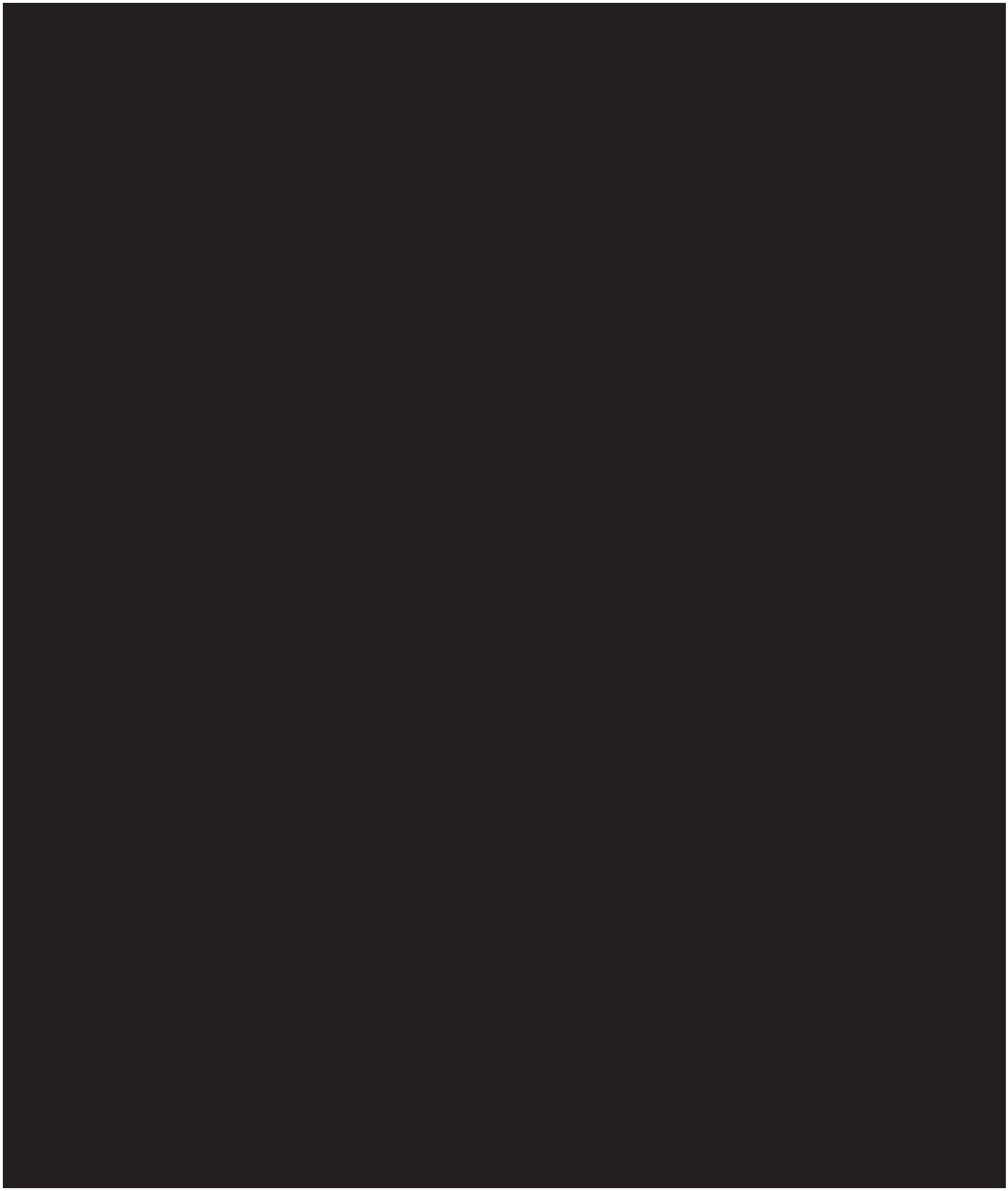
Untrimmed distal [s]iVaw at FRC, trimmed distal [s]iRaw at TLC and trimmed distal [s]iRaw at FRC will be analyzed as a supplementary analysis in the following way:

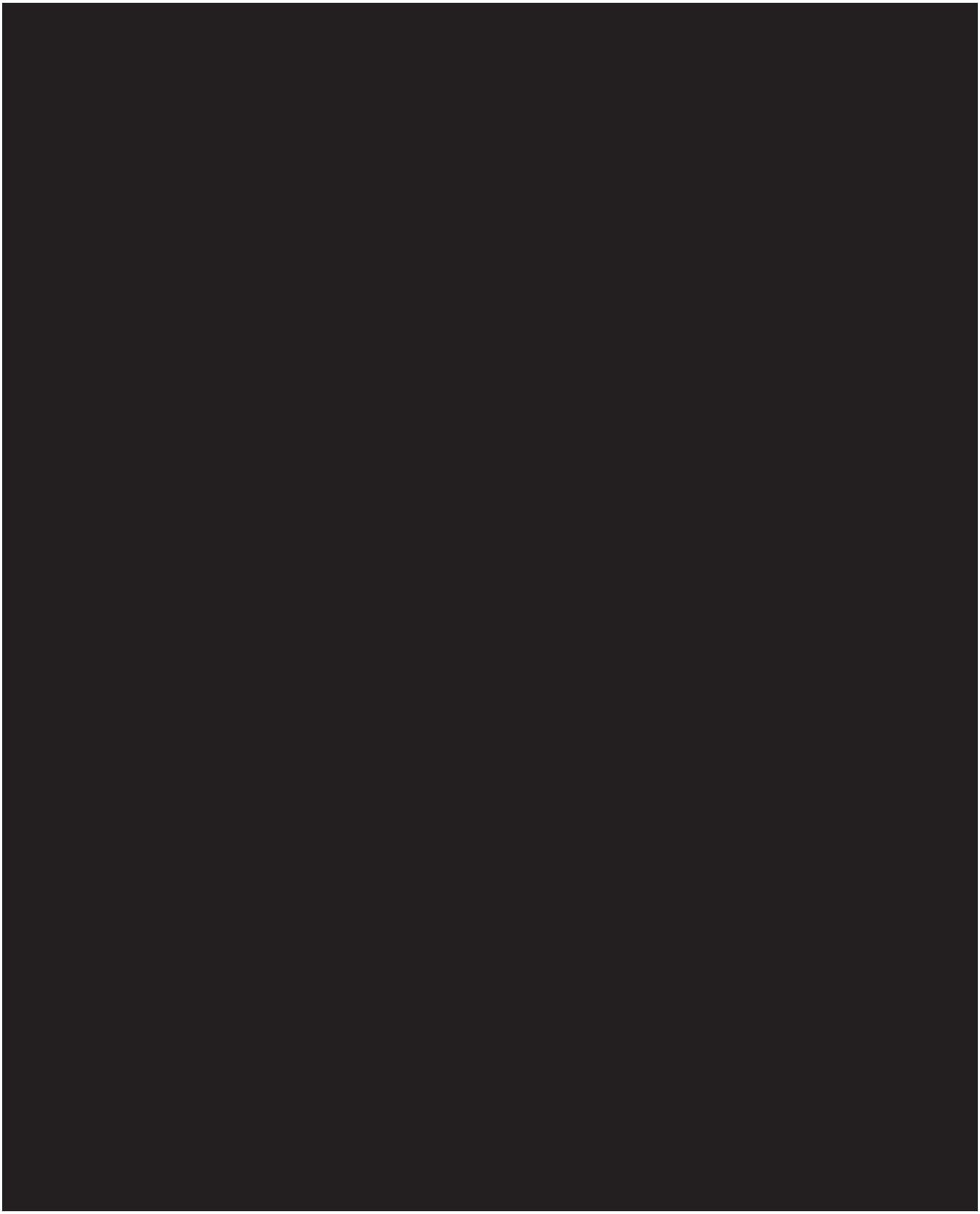
- Removing FRI data with technical issues

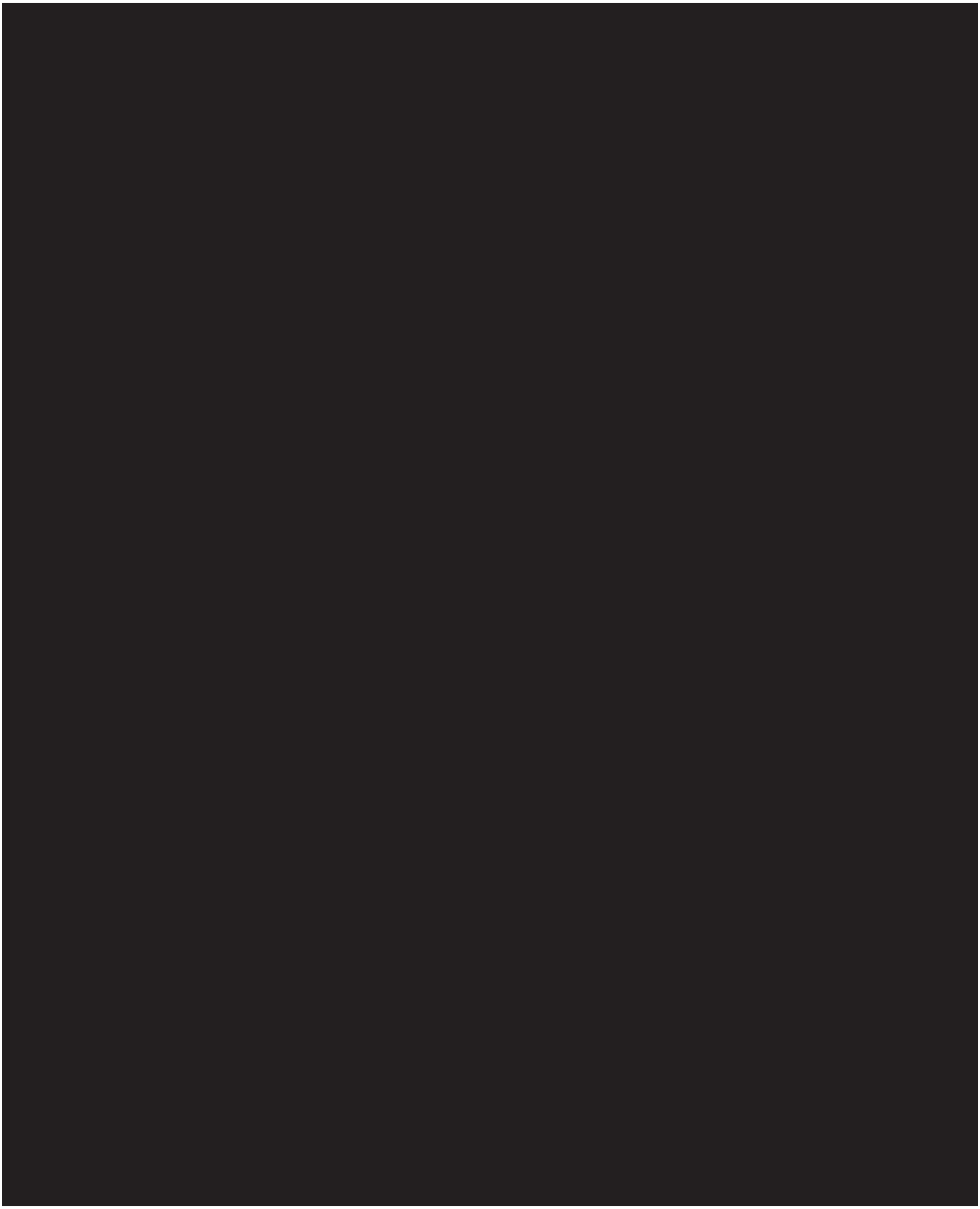
Percent change from baseline will be modelled using an MMRM model under the missing at random framework. The MMRM model will include study intervention (dupilumab, placebo), baseline value of the parameter, region (EE/ROW), ICS dose level (medium/high), visits (up to Week 24), study intervention by visit interaction, and baseline value by visit interaction terms all as fixed effects. An unstructured (UN) correlation matrix will be used to model the within-participant errors.

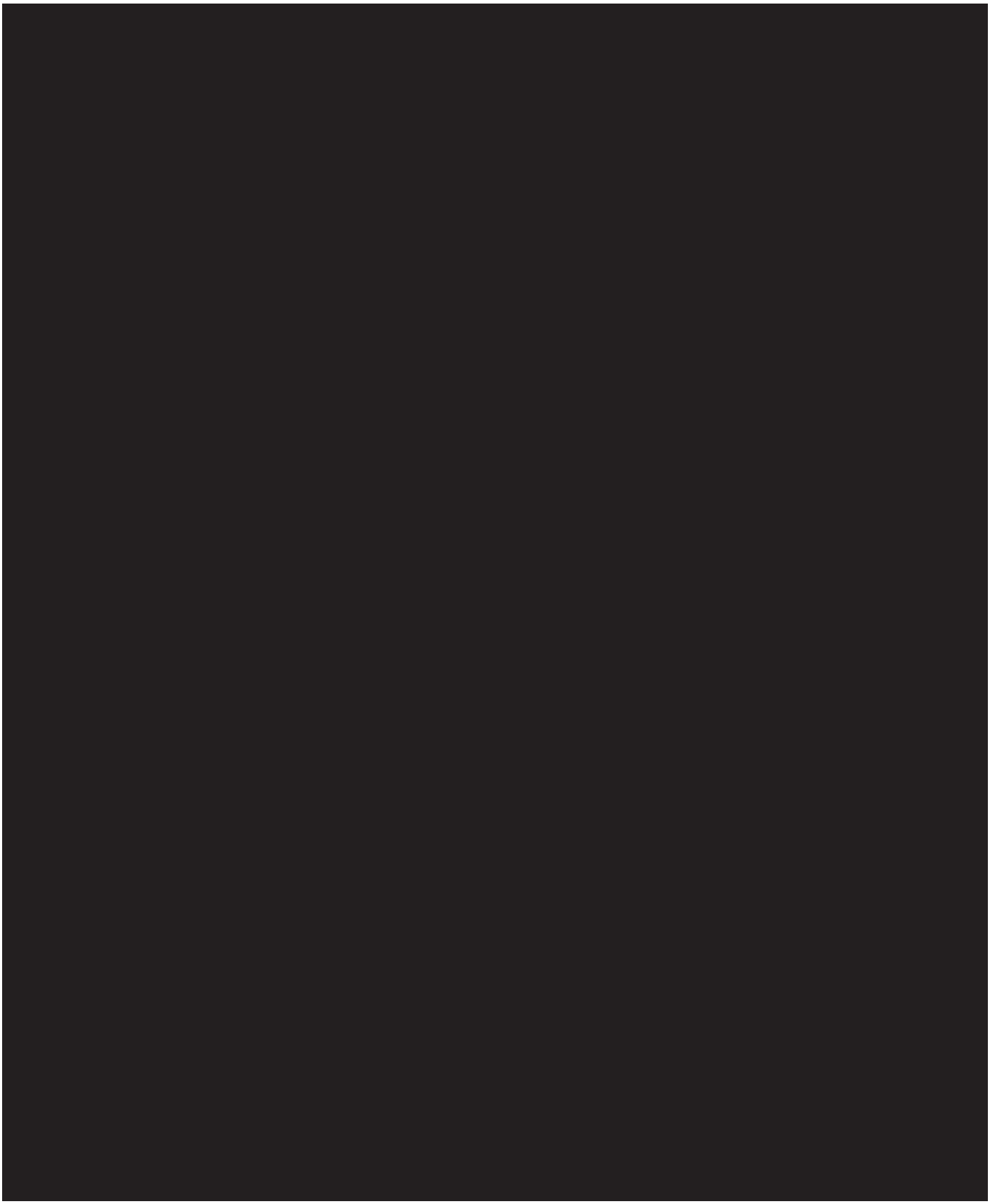
The same strategy as for MMRM model for primary endpoint untrimmed distal [s]iVaw will be used for the selection of the covariance structure if MMRM under unstructured correlation matrix fails to achieve convergence.











9. SAFETY ANALYSIS

All safety results will be summarized using the safety 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 +98 days and up to the end of the study follow-up.
- 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 adverse event reporting will be on TEAEs. Pre-treatment adverse events will be summarized separately.

All AEs will be coded by 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 15.4.5.

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, 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 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 AESI
- Any Serious AESI
- 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 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 (e.g., 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 TEAE 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 AE 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 patients 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 ≥5% in any study intervention group) by primary SOC, HLGT, HLT, and PT

Search criteria for COVID-19 related AE will be provided by SANOFI.

9.1.2. Relationship of adverse events to study intervention

The following TEAE summary will be generated.

- 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 summary will be generated.

- 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 (ie, mild, moderate, severe).

9.1.4. Serious adverse events

The following TEAE summaries will be generated.

- 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 summary will be generated.

- 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:

- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms).
- Anaphylactic reactions.
- Systemic hypersensitivity reactions.
- Helminthic infections.
- Keratitis
- Any severe type of conjunctivitis or blepharitis
- Significant Alanine Aminotransferase (ALT) elevation:
  - ALT >5 x ULN in participants with baseline ALT ≤2 x ULN;

    or

  - ALT >8 x ULN if baseline ALT >2 x 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,
  - Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE
  - Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

- 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 circumstances (ie, accidental or intentional) should be clearly specified in the overdose form.

The following TEAE summaries will be generated.

- 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 summary will be generated.

- 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.

- Number and percentage of participants who died during the trial by study period (ie, on study, pre-treatment period, TEAE period and post-treatment period).
- 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) including IgM HBcAb; hepatitis C virus antibodies (HCVAb). In case of results showing HBsAg (negative), and HBcAb (positive), an hepatitis B virus (HBV) deoxyribonucleic acid (DNA) testing will be performed to rule out a false positivity if the Investigator believes the participant is a false positive, 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), an hepatitis C virus (HCV) ribonucleic acid (RNA) testing may be performed to rule out a false positivity, if the Investigator believes the participant is a false positive.
- Human Immunodeficiency Virus (HIV) screening (Anti-HIV-1 and HIV-2 antibodies).
- Tuberculosis testing would only be performed 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 (in cells/µL) 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, Week 4, Week 12 and Week 24).

9.3. Vital sign measurements

Vital signs including weight, heart rate (HR), sitting systolic (SBP) and diastolic blood pressure (DBP), temperature and respiratory 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 using descriptive statistics for each visit or study assessment (baseline, each-post-baseline time point).

The Potentially Clinically Significant Abnormalities (PCSA) at any time during the TEAE period will be summarized 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 who have at least 1 assessment performed during the TEAE period. When a PCSA definition involves a change from baseline value, participants must also have a baseline value to be included in the summaries.

A listing of participants with at least 1 post-baseline PCSA will be provided and will display the participant's full profile (all participant's results) 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 of the direction).

9.4. Physical examination

There will be a physical examination at screening visit, at baseline visit (Day 1) before receiving the IMP and then at week 24 visit 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.

No analysis is planned for physical examinations.

9.5. Electrocardiogram

12-lead ECG will be obtained at screening visit using an ECG machine that automatically calculates HR (Heart Rate) and measures PR, QRS, QT, and QTc 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

Not applicable.

13.CHANGES IN THE PLANNED ANALYSIS

Not applicable.

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15.APPENDICES

15.1. Summary of statistical analyses

Table 15-1 Summary of statistical analyses

Endpoint	***Analysis Set***	***Primary analysis***	***Supportive analysis***	***Subgroup analysis***	***Estimands***
Primary endpoints					
Achievement of FeNO <25 ppb at Week 24 *(Dupilumab, placebo)*	*ITT*	*CMH test, (missing data considered as non-responders)*	*Sensitivity analyses: Repeat of Primary analysis based on multiple imputation analysis.* *Supplementary analyses: Repeat on primary analysis based on concomitant SCS use*	*Yes*	*Yes*
Untrimmed distal [s]iVaw at TLC: percent change from baseline to week 24 *(Dupilumab, placebo)*	*ITT*	*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 on primary analysis based on concomitant SCS use, based on participants having respected SABA washout period, and removing FRI data with technical issues*	*Yes*	*Yes*
Secondary endpoints					
Continuous variables	*ITT*	*Same approach as primary endpoint Untrimmed distal [s]iVaw at TLC*	*Supplementary analyses of pre-BD FEV_1:* *Removing potential outliers* *Using data borrowing approach* *Supplementary analyses for [s]iRaw at TLC and FRC and [s]iVaw at FRC removing data with technical issues*	*No*	*Yes (only for secondary endpoints included in the hierarchical testing procedure)*

Endpoint	***Analysis Set***	***Primary analysis***	***Supportive analysis***	***Subgroup analysis***	***Estimands***
Tertiary/Exploratory endpoints					
Continuous variables	*ITT*	*Same approach as primary endpoint Untrimmed distal [s]iVaw at TLC*	*No*	*No*	*No*
Composite endpoints	*ITT*	*Same approach as primary endpoint achievement of FeNO <25 ppb at Week 24*	*No*	*No*	*No*
Lung function parameters (post-BD FEV_1, pre-BD FEV_1), Imaging parameters (untrimmed distal [s]iVaw at TLC, untrimmed distal [s]iVaw at FRC, trimmed distal [s]iRaw at TLC, trimmed distal [s]iRaw at FRC, iVlobes at TLC, iVlobes at FRC, iV/Q at TLC, HRCT based IAD, iVaww at TLC, UCSF mucus scoring, HRCT based airway occlusions at FRC, mucus volume) and biomarker levels (FeNO)	*ITT*	*Correlation*	*No*	*No*	*No*

15.2. Schedule of study procedures

Procedure	Screening period 4 weeks ±1 week (21-35 days) before Day 1	Randomized Treatment Period (D: day; W: week) Visit windows after D1 are ±3 days				Post-treatment Follow-up
		D1	W4	W12	W24	up to W36[c]
Visit (V)	Screening visit V1	Baseline (randomization) visit V2			End of treatment visit[a, b] V5	End of follow up visit V6[d]
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demography	X					
Smoking status	X					
Medical/Surgical history	X					
Vital signs[e]	X	X	X	X	X	
Physical examination[f]	X	X			X	
Reversibility test[g]	X					
12-lead ECG	X					
ACQ-7[h]	X	X	X		X	
AQLQ(S)[i]		X			X	
FeNO[j]	X	X	X	X	X	
HRCT scan[k]		X	X		X	
Forced Oscillometry[l]		X	X	X	X	
Pre - bronchodilator FEV_1[m]	X	X	X	X	X	
Post - bronchodilator FEV_1[m]		X	X	X	X	
Pregnancy test (WOCBP only)[n]	X	X	X	X	X	X
Blood eosinophil count[o]	X	X	X	X	X	
Hepatitis B, C and HIV Serology tests[p] Tuberculosis testing[q]	X					

Procedure	Screening period 4 weeks ±1 week (21-35 days) before Day 1	Randomized Treatment Period (D: day; W: week) Visit windows after D1 are ±3 days				Post-treatment Follow-up
		D1	W4	W12	W24	up to W36[c]
Visit (V)	Screening visit V1	Baseline (randomization) visit V2			End of treatment visit[a, b] V5	End of follow up visit V6[d]
Home dosing diary Asthma background therapy diary[r]		X	X	X	X	
Randomization		X				
IVRS/IWRS call	X	X	X	X	X	X
Investigational product administration[s]		X	X	X	X	
Drug dispensation		X	X	X		
Prior and concomitant medication review	X	X	X	X	X	X
AE/SAE/AESI review	X	X	X	X	X	X

ACQ-7=7 item-Asthma Control Questionnaire; AE=Adverse Event; AESI=Asthma Quality of Life Questionnaire with Standardised Activities; ATS= American Thoracic Society; ECG=Electrocardiogram; ESD= Early Study Discontinuation; ETD=Early Treatment Discontinuation; FeNO=Fractional exhaled nitric oxide; FEV1=Forced expiratory volume in 1 second; FOT= Forced oscillation technique; HRCT= High-resolution computed tomography; IVRS=Interactive voice recognition system; IWRS= Interactive web response system; SAE=Serious Adverse Event;

a Patients who prematurely discontinue the study intervention (prior to completing the 24-week treatment period) should attend an Early Treatment Discontinuation (ETD) visit at earliest convenience with all the assessments planned for the End of Treatment visit (V5), except HRCT scans and IMP. In particular cases when the ETD visit is closed to a regular study visit, ETD could be merged and will replace the regular visit. In addition, the patients will be asked and encouraged to complete all the remaining study visits according to the visit schedule until and including the EOT visit (V5). Under exceptional circumstances when a patient 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 medication should be collected.

b Patients who prematurely discontinue the study should attend an Early Study Discontinuation (ESD) visit at earliest convenience with all the procedures planned for the End of Treatment Visit (Visit 5) except IMP. If the Investigator considers that the time from the last HRCT scan exposure is not acceptable, the investigation will not be done.

c Post-treatment Follow-up: up to 12 Weeks or until the patients switch to commercialized dupilumab (or other biologic products), whatever comes first.

d Visit 6 will be a telephone visit. For the patients who switch to commercialized dupilumab (or other biologic products), the call visit should be done prior to the first injection with commercialized dupilumab (or other biologic products).

e Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius).

f A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and neurological systems and will be performed at V1, V2 and V5. Body weight (kg) will be measured at V1, V2 and V5. Height (cm) will be measured only at V1.

g Reversibility test: Three attempts may be performed during the screening period to meet the qualifying criteria for reversibility before randomization. This is only required if a reversibility test meeting eligibility criterion was not performed within 6 months prior to Visit 1.

h Asthma Control Questionnaire-7 (ACQ-7): items 1 to 6 should be completed by the patient, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire should be completed by the patients before the consultation and/or clinical tests, in a quiet place. ACQ-5 scores (mean of the responses to the

first 5 questions) and ACQ-6 (mean of the responses to the first 6 questions) will be derived from ACQ-7. The local values of FEV1 will be considered for the ACQ-7 scores. For the statistical analysis we will use centrally read values.

i Asthma Quality of Life Questionnaire with Standardised Activities [AQLQ(S)] should be completed by the patient, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire should be completed by the patients before the consultation and/or clinical tests, in a quiet place.

j FeNO should be conducted prior to spirometry and the patient should refrain from eating and drinking for ≥1 hour before the procedure. The test will be performed after a wash out period of bronchodilators according to their action duration as detailed in protocol (Table 4 (Section 8.1)). Retesting of FeNO can be done one additional time during screening if the eligibility criterion for FeNO was not met at V1. FeNO will be rechecked at randomization visit (V2) for eligibility. Further details on the procedure for measuring FeNO will be provided in a separate instruction manual

k Centrally read. Scans are respiratory gated to avoid variations in lung and airway volume, as per scans protocol. Further details on the HRCT scan will be provided in a separate instruction manual. The wash out time of the asthma controllers and rescue medication before HRCT and lung function assessments is detailed in protocol (Table 4 (Section 8.1)). If HRCT scan can't be performed at D1 due to logistic reasons, it can be scheduled the next day. In this particular situation the investigator should ensure that the IMP loading dose is administered after the HRCT scan, at D1+1 day. At visits, the HRCT scan can be done before spirometry or before post-BD FEV_1 or after (in the latter case the wash-out period of SABA should be ensured), as per Investigator's decision.

l FOT should be conducted prior to spirometry. Further details on FOT will be provided in a separate instruction manual.

m Centrally read. Spirometry test should be performed before IMP administration, in the morning if possible, but 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 as detailed in protocol (Table 4 (Section 8.1)). This will be verified before performing the measurements. A patient who is unable to complete a successful spirometry effort as defined by ATS criteria or evaluated by the investigator or didn't meet the eligibility criterion for pre-BD FEV_1 at V1 can be retested one additional time during the screening period. For spirometry the investigator will assess the eligibility based on the FEV1 local values from V1 and V2 before randomization (the results from central reading will not be available on the same day). The recommendation is to perform the FeNO and FOT before spirometry

n Serum pregnancy test at screening visit (Visit 1) and urine pregnancy tests at the other visits using dipstick. A negative result must be obtained at Visits 1 and 2 for eligibility. 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 end of follow-up visit.

o Retesting of eosinophil count is allowed up to three times during the screening period to meet inclusion criteria for showing eosinophil count ≥300 cells/microliter (cells/µL) (I 06) before randomization. This is only required if the patient doesn't have the blood eosinophil count measured within 6 months prior to V1 in the absence of OCS treatment.

p Hepatitis screening covering hepatitis B surface antigen (HBs Ag), total hepatitis B core antibody (total HBcAb) including IgM 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 (HIV) screening (Anti-HIV-1 and HIV-2 antibodies).

q Tuberculosis (TB) testing would only be performed on a country by country basis according to the routine clinical practice and the local guidelines if required by Regulatory Authorities or Ethics Committees.

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

s 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 (patient, caregiver, or health care professional) or in a health care facility. At D1, loading dose dupilumab arm 600 mg (300 mg x 2 syringes/injections); 2 placebo syringes for the placebo arm. In case that the HRCT scan is performed one day after D1 due to logistic reasons, the IMP loading dose should be administered after the completion of HRCT scan (D1 +1 Day).

NOTE:
• The contingency measures for a regional or national emergency declared by a governmental agency are detailed in Appendix 9 of the protocol (Section 10.9).
• In case of severe asthma exacerbations treated with systemic corticosteroids, the visits can be postponed up to 1 week to ensure the wash-out period (protocol Table 4) is completed before performing HRCT scan, FeNO, FOT, and spirometry. In case this is not possible (eg, a patient experiences an exacerbation shortly before the scheduled visit), the procedures can be performed as planned, but it should be recorded that the patient had recently taken systemic corticosteroids.

15.3. Missing efficacy data

Asthma Control Questionnaire (ACQ-7, ACQ-6 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.

Asthma Quality of Life Questionnaire (AQLQ)

- 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.

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 study intervention or after the study intervention 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 15-2 Analyses window definition

Scheduled visit post-baseline	Targeted study day*	Visit window		
		AQLQ(S)	FRI and ACQ	Biomarkers, Forced Oscillometry, Spirometry and Vital signs
Week 4 (Visit 3)	29		[2, 98]	[2, 56]
Week 12 (Visit 4)	85			[57, 126]
Week 24 (Visit 5)	169	[2, ∞]	[99, ∞]	[127, ∞]

* 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).

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 (ie, 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 15-3 Search criteria for AESI

AESI	Search Criteria
Anaphylactic reactions	Anaphylactic reactions: includes anaphylactic reaction narrow SMQ (20000021) terms and programmatic identification of cases based on occurrence of at least two preferred terms meeting the algorithm criteria occurring within 2 consecutive days of each other
Systemic hypersensitivity reactions	SMQ: Hypersensitivity [Narrow]
Helminthic infections	HLTs of "Helminthic infections NEC"
Keratitis	PTs of • Keratitis, Allergic keratitis • Corneal infection • Ulcerative keratitis • Atopic keratoconjunctivitis • Herpes ophthalmic • Ophthalmic herpes simplex
Any severe type of conjunctivitis or blepharitis	1. Conjunctivitis is defined as the following PTs with intensity "severe" in eCRF AE page: • Adenoviral conjunctivitis • Conjunctival irritation • Conjunctival oedema • Conjunctival ulcer • Conjunctivitis • Conjunctivitis allergic • Conjunctivitis chlamydial

AESI	Search Criteria
	• Conjunctivitis gonococcal neonatal • Conjunctivitis tuberculous • Conjunctivitis viral • Giant papillary conjunctivitis • Inclusion conjunctivitis • Ophthalmia neonatorum • Seasonal allergy • Herpes simplex virus conjunctivitis neonatal • Conjunctival hyperaemia • Inclusion conjunctivitis neonatal • Conjunctivitis bacterial • PingueculitisPhotoelectric conjunctivitis • Oculorespiratory syndrome • Acute haemorrhagic conjunctivitis • Blebitis • Ligneous conjunctivitisNoninfective conjunctivitis • Oculoglandular syndrome • Conjunctivitis fungal • Conjunctival suffusion • Giant fornix syndrome 2. Blepharitis is defined as the following PTs with intensity “severe” in eCRF AE page: • Abscess of eyelidBlepharitis • Blepharitis allergic • Blepharochalasis • Chalazion • Dacryoadenitis acquired • Dacryocanaliculitis • Dacryocystitis • Eczema eyelids • Erythema of eyelid • Eyelid boil • Eyelid infection • Eyelid oedema • Hordeolum • Lacrimal sac cellulitis • Meibomianitis • Swelling of eyelid • Swollen tear duct • Lid margin discharge • Meibomian gland discharge • Eyelid margin crusting • Bacterial dacryocystitis • Eyelid folliculitis • Eyelid irritation • Eyelid cyst • Meibomian gland dysfunction • Inflammation of lacrimal passage • Eyelid rash

AESI	Search Criteria
	• Staphylococcal blepharitis • Bacterial blepharitis • Lacrimal gland abscess • Demodex blepharitis
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 15-4 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 Control Questionnaire (ACQ-7, ACQ-6 and ACQ-5)

Asthma Control Questionnaire-7 (ACQ-7) 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) and a scoring of the FEV_1% predicted by clinic staff, also on a 7-point scale.

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 ACQ-7 has 7 questions with the first 5 items assessing the most common asthma symptoms (corresponding to ACQ-5),

The first 5 items assess the most common asthma symptoms:

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
6. short-acting bronchodilator use
7. FEV_1 % predicted

The first 6 items will be used directly according to the result recorded on the 7-point scale (0 = no impairment to 6 = maximum impairment).

For Item 7, the Percent predicted FEV_1 value will be used and converted into the same 7-point scale, according to the following table:

FEV_1% predicted	**Score**
>95% predicted	0
95-90%	1
89-80%	2
79-70%	3
69-60%	4
59-50%	5
<50% predicted	6

A global score is calculated: the questions are equally weighted and the ACQ-7 score is the mean of the 7 questions and, therefore, 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-7, 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 ACQ-7 on paper. Asthma Control Questionnaire Items 1 to 6 should be completed by the participant, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire

should be completed by the participants before the consultation and clinical tests, including spirometry, in a quiet place.

The local values of FEV_1 will be considered for the ACQ-7 scores. For the statistical analysis we will use centrally read values.

ACQ-5 scores (mean of the responses to the first 5 questions) and ACQ-6 (mean of the responses to the first 6 questions) will be derived from ACQ-7.

Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S])

AQLQ[S] was designed as a self-administered participant reported outcome to measure the functional impairments that are most troublesome to adolescents ≥12 years of age and adults as a result of their asthma. The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
  - 6 - Chest Tightness
  - 8 - Short of Breath
  - 10 - Wheeze
  - 12 - Coughing
  - 14 - Chest Heaviness
  - 16 - Clear Your Throat
  - 18 - Difficulty Breathing Out
  - 20 - Wake Up with Asthma Symptoms
  - 22 - Heavy Breathing
  - 24 - Woken at Night
  - 29 - Interference with a Good Night
  - 30 - Fighting for Air
- Activity limitation (11 items)
  - 1 - Strenuous Activities
  - 2 - Moderate Activities
  - 3 - Social Activities
  - 4 - Work/School-Related Activities
  - 5 - Sleeping
  - 11 - Avoid Cigarette Smoke
  - 19 - Avoid Dust
  - 25 - Avoid Weather Pollution Outside
  - 28 - Avoid Strong Smells or Perfume
  - 31 - Overall Range of Activities
  - 32 - All the Activities
- Emotional function (5 items)
  - 7 - Having Asthma

13 - Frustrated
15 - The Need to Use Medication
21 - Asthma Medication Not Available
27 - Getting Out of Breath

- Environmental Stimuli (4 items)
  9 - Exposure to Cigarette Smoke
  17 - Exposure to Dust
  23 - Weather or Air Pollution Outside
  26 - Exposure to Strong Smells

The overall AQLQ[S] score is the mean of all 32 responses and the individual domain scores are the means of the items in those domains. Higher scores indicate better quality of life. The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (participant interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (28).

The participants will complete the AQLQ(S) on paper. AQLQ[S] should be completed by the participant, independently from their physician, the study nurse or any other medical personnel and without any help from friends or relatives. The questionnaire should be completed by the participants before the consultation and clinical tests, including spirometry, in a quiet place.

15.9. Spirometry

A spirometer that meets the 2019 ATS/European Respiratory Society (ERS) recommendations will be used.

For pre-BD measured parameters, including FEV_1 and FVC spirometry will be performed before IMP administration and after withholding the standard of care asthma treatment.

For post-BD FEV_1, 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 same spirometer 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; however, if necessary to undertake the testing with the participant standing or 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 every visit. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a

participant fails to provide repeatable maneuvers, an explanation should be recorded in the e-CRF. At least 2 acceptable curves must be obtained.

The largest FEV_1 and largest FVC should be recorded after the data are examined from all of the acceptable curves, 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 study participant is seen, and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (ie, 3-liter syringe) that is used to calibrate the spirometer 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 did not meet the eligibility criterion for pre-BD FEV_1 at V1 can be retested one additional time during the screening period of the study. The spirometry will be centrally read. The locally read values of FEV_1 will be considered for the participant qualification into the study at V1 and V2.

For the statistical analysis centrally read values will be used.

15.10. Functional Respiratory Imaging (FRI)

Functional Respiratory Imaging is a non-invasive measurement of the participant specific respiratory system. A set of distinct imaging parameters analyzes exposure, structure and function of the lungs and airways in asthma.

The process starts with the acquisition of low dose, pre-BD HRCT scans of the participant. The measurements are performed on the segmented 3-dimensional geometries from these scans. Computational fluid dynamics (CFD) is used to quantify airflow and exposure.

HRCT scans will be used to generate FRI measurements allowing for an evaluation of regional asthma disease manifestation and treatment effect. These CT images are taken during breath hold at two distinct lung levels: at the end of a normal exhalation (functional residual capacity; FRC) and at the maximal inspiration (total lung capacity; TLC).

The following FRI parameters, based on low-dose inspiratory-expiratory multi-slice computed tomography images and computational fluid dynamics flow simulations will be analyzed:

- Lobar volumes at FRC and TLC
- (specific) airway volumes at FRC and TLC
- (specific) airway resistance at FRC and TLC
- (percent predicted) internal lobar airflow distribution
- Blood vessel density at TLC
- (specific) airway wall volume at TLC
- Air trapping at FRC
- Ventilation/perfusion ratio
- UCSF mucus scoring
- Mucus volume
- PI10 (change from baseline)

- Airway wall area (change from baseline)
- Wall area percentage (change from baseline)
- Airway radius (change from baseline)

FRI parameters are assessed in the following different zones of the respiratory system:

- Overall lung (except for HRCT based IAD)
- Distal lung (only for [s]iVaw, [s]iRaw and iVaww)
- Central lung (only for [s]iVaw, [s]iRaw and iVaww)
- Right upper lobe (RUL)
- Right middle lobe (RML)
- Right lower lobe (RLL)
- Left upper lobe (LUL)
- Left lower lobe (LLL)

However, the possibility exists that for some participants no distinction can be made between the different lung lobes. In this case, the following zones can also be identified:

- Right upper and middle lobe (RUL+RML)
- Right middle and lower lobe (RML+RLL)
- Right upper and lower lobe (RUL+RLL)
- Right upper, middle and lower lobe (RUL+RML+RLL)
- Left upper and lower lobe (LUL+LLL)

As the visible area on the scanner can vary from one visit to another, the results can be trimmed (use only generations of airways that are visible in all the scans for each segment) in order to keep only the area common to the different visits, or untrimmed (use all the generations visible at the particular study visit scan for each segment). Trimmed and untrimmed data will be available.

Specific Airway Volume ([s]iVaw):

(s)iVaw is the change of volume of the airways (in mL), taking into account the lung volume changes (in L) as well. It corresponds to the ratio between the airway volume (iVaw) and the lobar volume.

Specific Airway Resistance ([s]iRaw):

(s)iRaw is defined as the pressure drop over the flow rate of the fluid. The unit is [kPa/(L/s)]) or [kPa*s/L].

Mucus score:

University of California, San Francisco (UCSF researchers (John Fahy's research group) have developed a new method to measure the burden of intraluminal mucus using Multi-detector Computed Tomography (MDCT) by quantifying the number of bronchopulmonary segments that are completely occluded with mucus.

Airway wall volume:

Asthmatics have increased airway wall volumes due to inflammation compared to healthy individuals. The airway wall volume/airway lumen ratio parameter can be derived from the FRI parameters airway wall volume and airway volume. Airway wall thickness can be derived from this as well (and can be shown in discrete locations).

Lobar volumes:

By identifying and grouping the voxels that represent the air in the lungs, the lung volume (L) can be determined from the scans at both FRC and TLC. During segmentation, identifying the fissure planes on the CT images and using these surfaces as cutting objects can separate lung lobes. Therefore, not only the total lung volume is determined, but also the volume of each lobe individually, which allows to pick up substantial regional physiological changes of the airways and the lobe volumes.

Airway dilation:

Airway dilation is defined as the difference between the trimmed airway volume at week 24 and the trimmed airway volume at baseline.

Airway recruitment:

Airway recruitment is defined as the difference between the untrimmed airway volume at week 24 and the untrimmed airway volume at baseline and the airway dilation.

Pi10:

Pi10 represents the average airway wall thickness normalized to a ‘theoretical’ airway lumen of 10-mm inner perimeter. This endpoint is calculated from a segmental level (distal airway zone).

Airway wall percentage:

Airway wall percentage represents the wall area as a percentage of the sum of wall area and the airway lumen area. This endpoint will be calculated for central, distal and for each of the 5 lobes.

Airway wall area:

The airway wall area represents the average area per zone of the airway wall, and will be calculated for central, distal and for each of the 5 lobes.

Airway radius:

Airway radius represents the average per zone of the airway radius from centerline to airway wall. This endpoint will be calculated for central, distal and for each of the 5 lobes.

Mucus volume:

Mucus volume is the total volume of all detectable mucus plugs, which are defined as a complete occlusion of the airway, at TLC.

15.11. Forced Oscillometry (FOT)

The FOT determines breathing mechanics by superimposing small external pressure signals on the spontaneous breathing of the participant. It is indicated as a diagnostic method to obtain reliable differentiated tidal breathing analysis. R5 represents the total resistance of the airways. R20 represents resistance of the large, or proximal, airways. R5 − R20 is an indirect measure of the resistance in the small airways, which refers to freq dependence of resistance 5-20Hz.

FOT should be conducted prior to spirometry and HRCT scan. The assessment will be done by local reading.

Area of Reactance:

Area of reactance (AX) is the integrated low frequency respiratory reactance magnitude between 5 Hz and Fres (Resonant frequency). Resonant frequency (Fres) indicates the frequency at which the inertial properties of the airways and capacitance of lung periphery are equal. Total reactance at this point is zero. Normal Fres is 6–11 Hz. Fres increases in peripheral airway obstruction and fibrosis.

AX relates to respiratory compliance, small airway patency and correlates with R5–R20.

15.12. Biomarkers

Fractional exhaled nitric oxide (FeNO) will be analyzed using a NIOX instrument using a flow rate of 50 mL/s, and reported in ppb. This assessment should be conducted prior to spirometry, FOT and HRCT scan and the participant should refrain from eating and drinking for at least 1 hour prior to the procedure.

15.13. Rescue and Prohibited Medications.

Rescue medications (ie, 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 the following medications is considered as prohibited:

- Immunosuppressants and biologic therapy within 3 months prior to V1 until EOT (V5)
- Treatment with live (attenuated) vaccine within 4 weeks before V1 until the end of study
- Treatment with systemic corticosteroids within 2 weeks prior to V1, during screening and randomized study intervention period. Systemic corticosteroids can only be used to treat an asthma exacerbation during the randomized study intervention period and are not allowed to be used for other conditions.

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16. SIGNATURE PAGE

Client:	**SANOFI**
Protocol number:	LPS15834

Document description:	Final Statistical Analysis Plan
SAP title:	Randomized, double blind, placebo controlled study to evaluate the effect of dupilumab on airway inflammation through assessments of lung function, mucus plugging and other lung imaging parameters in patients with asthma
SAP version number:	Final Statistical Analysis Plan, Version 2.0
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For PPD: [redacted]
For SANOFI: [redacted]

Approved by:

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Approve & eSign	[redacted]
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