



## STATISTICAL ANALYSIS PLAN

**An exploratory, randomized, double-blind, placebo-controlled study of the effects of dupilumab on airway inflammation of adults with persistent asthma**

**SAR231893 (REGN68)-PDY14192**

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-5:	Asthma control questionnaire 5-question version
ADA:	Anti-drug antibody
AESI:	Adverse events of special interest
ALT:	Alanine aminotransferase
ANA:	Anti-nuclear antibody
ANCOVA:	Analysis of covariance
AST:	Aspartate aminotransferase
ATC:	Anatomic category
BALF:	Bronchoalveolar lavage fluid
CI:	Confidence interval
CPK:	Creatine phosphokinase
CRF:	Case report form
CSR:	Clinical Study Report
CV:	Coefficient of variation
EOT:	End of treatment
FDR:	False discovery rate
FEF:	Forced expiratory flow
FeNO:	Fractional exhaled nitric oxide
FEV <sub>1</sub> :	Forced Expiratory Volume in One Second
FVC:	Forced vital capacity
HLGT:	High level group term
HLT:	High level term
ICC:	Immunocytochemistry
ICS:	Inhaled corticosteroid
IHC:	Immunohistochemistry
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
LABA:	Long-acting beta-agonists
LAMA:	Long-acting muscarinic antagonist
LFT:	Liver function test
LLT:	Lower level term
LS:	Least square
MBP:	Major basic protein, Major basic protein
MDI:	Metered dose inhaler
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	Mixed-effect model with repeated measures
NAb:	Neutralizing antibody
NSAID:	Nonsteroidal anti-inflammatory drug
OLE:	Open label extension
PCSA:	Potentially clinically significant abnormality
PD:	Pharmacodynamics

PEF:	Peak Expiratory Flow
PK/PD:	Pharmacokinetic-pharmacodynamics
ppb:	Parts per billion
PT:	Preferred term
q2w:	Every 2 weeks
SAE:	Serious adverse event
SAP:	Statistical analysis plan
SC:	Subcutaneously
SD:	Standard deviation
SEM:	Standard error of the mean
SMQ:	Standardized MedDRA query
SOC:	System organ class
TEAE:	Treatment-emergent adverse event
Th2:	T-helper cell 2
ULOQ:	Upper limit of quantification
WHO-DD:	World Health Organization-Drug Dictionary

## **1 OVERVIEW AND INVESTIGATIONAL PLAN**

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical techniques to be used to analyze the data for SAR231893 (REGN668) study protocol PDY14192 approved on 23 November 2016 (amended protocol 02). The purpose of the SAP is to ensure the credibility of study findings by pre-specifying statistical approaches to the analysis of study data prior to the database lock.

### **1.1 STUDY DESIGN AND RANDOMIZATION**

PDY14192 is a Phase 2a, exploratory, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study of repeated doses of dupilumab or placebo administered subcutaneously (SC) every 2 weeks (q2w) for 12 weeks in adult patients with persistent asthma who are receiving at minimum a medium to high dose of inhaled corticosteroid (ICS) in combination with long-acting beta-agonists (LABA). Patients requiring a third asthma controller are eligible. Both the patients and investigators will be blinded to assigned active drug or matching placebo.

After a screening phase of up to 6 weeks (5 weeks and optional addition of 7 days), patients will be centrally randomized (using allocation from block randomization schedule) via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 1:1 randomization ratio to dupilumab 300 mg q2w in 2 mL or placebo q2w in 2 mL. Randomization will be stratified by ICS dose level (medium, high) and region (North America, Europe).

During the study, patients will undergo 2 bronchoscopy procedures (one prior to the initiation of study drug and the other after 12 weeks of treatment) for the collection of bronchial biopsy, bronchial brushing and bronchoalveolar lavage fluid samples.

Approximately 42 patients will be randomized to dupilumab or placebo (around 21 patients per group) with at least 21 patients receiving treatment with high dose of ICS and no more than 8 patients with baseline blood eosinophils < 150 cells/ $\mu$ L (i.e., 0.15 Giga/L).

### **1.2 OBJECTIVES**

#### **1.2.1 Main objectives**

The main objective of this study is to evaluate the effect of dupilumab, compared to placebo, on airway inflammation in patients with persistent asthma.

#### **1.2.2 Additional objectives**

The additional objective of this study is to assess safety, tolerability and immunogenicity of dupilumab compared to placebo.

### 1.2.3 Exploratory objectives

Exploratory objectives of this study include the following:

- To explore the effects of dupilumab, compared to placebo, in patients with persistent asthma on:
  - Pulmonary function and asthma control;
  - T-helper cell 2 (Th2)-associated biomarkers in peripheral blood.
- To explore the pharmacokinetic-pharmacodynamics (PK/PD) relationship of the inflammatory biomarkers.
- To evaluate the relationship between the baseline characteristics of patients (e.g., demographics, clinical status, clinical lab values, biomarkers, and genetic profiles) and treatment responses.

### 1.3 DETERMINATION OF SAMPLE SIZE

The sample size and the statistical power are estimated based on the pharmacodynamics (PD) endpoint of fractional exhaled nitric oxide (FeNO) as a surrogate marker for airway inflammation as no historical data was available on the main endpoints of bronchial inflammatory cells at the time of the protocol writing no historical data is available on the main endpoints of bronchial inflammatory cells.

The following assumptions are used for the estimations:

- A difference of 25 parts per billion (ppb) in the change from baseline in FeNO at Week 12/end of treatment (EOT) between dupilumab and placebo, and a common standard deviation (SD) of 32 ppb (this corresponds to a hypothesized effect size of 0.78)
- A t-test at 1-sided  $\alpha=0.05$
- Not accounting for early dropout, i.e., the calculated sample size refers to the number of completers who have baseline and Week 12/ EOT bronchoscopy measurements and have adequate biopsies (i.e., of sufficient quality, from which quantitative results are available for at least one of the biomarkers tested) for analysis at both baseline and Week 12/EOT.

Based on above assumptions, it is estimated that, with a total of 42 completers with adequate biopsy samples (21 completers per group), the study will have an 80% power to detect a difference of 25 ppb in the change from baseline in FeNO at Week 12/EOT between dupilumab and placebo.

Based on observations in other clinical trials (see Section 9.5 of the study protocol), it is expected that this sample size will be sufficient to evaluate the main PD endpoints in bronchial submucosa. Brightling et al (1) powered their study to show a reduction in airway submucosal eosinophils from baseline to Week 12 for their active drug compared with placebo using the following SD of the log values of the ratio vs. baseline in the change in number of eosinophils per mm<sup>2</sup> of subepithelial tissue in bronchial biopsy: 1.62 for the active group and 1.82 for placebo

Using an estimate of the SD of the log of the ratio in both groups of 1.7, it is calculated that 21 patients per group (planned sample size of the PDY14192 study) would be sufficient to detect a 3.8-fold decrease (corresponding to a hypothesized effect size of 0.78 in log of ratio) compared with placebo with 80% power (one-sided test at 5%).

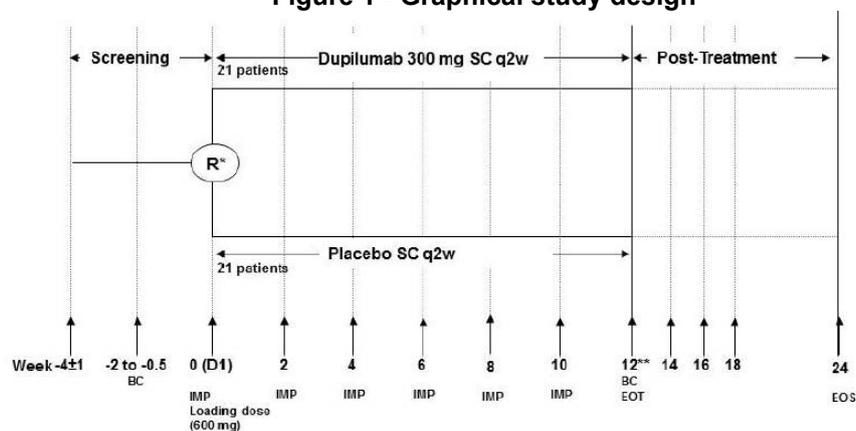
The calculations were made using nQuery Advisor 7.0.

## 1.4 STUDY PLAN

The clinical trial consists of three periods:

- **Screening Period** (5 weeks and potentially additional up to 7 days): to determine a patient's eligibility status or scheduling of bronchoscopy and establish the level of asthma control before randomization. During the screening period, a bronchoscopy procedure is performed to acquire baseline samples.
- **Randomized Treatment Period** (12 weeks and potentially additional up to 4 weeks in the case the bronchoscopy at week 12 has to be postponed to week 14 or 16): to treat with dupilumab or placebo SC injection.
- **Post-treatment Period** (12 weeks): to monitor patients' statuses when off study drug treatment for patients not participating in the open label extension (OLE) LTS12551 study. Eligible patients participating in the OLE study will enter the study after completion of the EOT visit assessments. The post-treatment analyses for patients who enter the OLE study will be described in a separate SAP.

Figure 1 - Graphical study design



\*R: Randomization 1:1  
BC: Bronchoscopy  
IMP: Investigational Medicinal Product administration  
EOT: End-Of-Treatment visit  
EOS: End-Of-Study visit  
Visit windows for visits after Day 1 are +/- 3 days  
\*\*If a patient is unable to undergo a bronchoscopy at Week 12, the EOT visit may be postponed and up to 2 additional doses of IMP may be administered.

Refer to the [Appendix A](#) for the detailed study flow chart.

## 1.5 MODIFICATIONS FROM THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section. These changes are not based on any unblinded study data.

The protocol history table below gives rationale and key details of major changes to the protocol statistical section.

**Table 1 – Protocol amendment statistical changes**

<b>SAP section</b>	<b>Rationale</b>	<b>Description of statistical changes</b>
2.2.1 Pharmacodynamic populations	To identify a single bronchoscopy PD population for bronchoscopy biomarkers, and a secondary PD population for other PD biomarkers.	<p><u>The following text:</u> For the main PD endpoints in bronchial submucosa, the PD population will consist of all randomized patients who underwent baseline and Week12/EOT bronchoscopies and have adequate biopsies for analysis at both baseline and end of treatment. (...) Analysis population for additional PD/biomarker endpoints will be similarly defined.</p> <p><u>Was replaced by:</u> Two PD populations will be defined: - The bronchoscopy PD population will encompass all randomized and treated patients with an evaluable bronchoscopy performed at baseline and at Week 12/EOT. - The secondary PD population will encompass all randomized and treated patients.</p>
2.2.2 Efficacy population	To harmonize the population for efficacy analyses across all endpoints	<p><u>The following text:</u> For analyses of exploratory efficacy endpoints, the efficacy population will consist of all randomized patients who have both baseline and a post-baseline spirometry data. The analysis will be “as-treated” or based on the treatment actually received. If a patient receives in error both placebo and dupilumab during the course of the study, the patient will be included in the dupilumab group. Additional exploratory efficacy analyses will be also performed using the conventional mITT population in which patients will be included in the group as randomized.</p> <p><u>Was replaced by:</u> Exploratory efficacy analyses will be performed on the secondary PD population.</p>
2.2.3 Safety population	To harmonize the definition of the safety population to be consistent with EFC13579 study	<p><u>The following text:</u> The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.</p> <p><u>Was replaced by:</u> Patients treated without being randomized will be included in the safety population.</p>

SAP section	Rationale	Description of statistical changes
2.6.1 Description of pharmacodynamic variables	To comprehensively describe the biomarkers that will be collected and analyzed in the study	All bronchoscopy and blood biomarkers are listed by matrix and type of biomarkers. Normalization of mRNA data after RT-qPCR to housekeeping genes is detailed
2.6.2.3 Main analyses: pharmacodynamic analyses	To take into account that for some PD variables, the ratio from baseline is also a parameter of interest, in addition to the absolute change from baseline	Absolute change from baseline and ratio from baseline will be derived for some biomarkers
2.6.2.3 Main analyses: pharmacodynamic analyses	To describe the formal statistical analyses done on FeNO data	A MMRM approach will be implemented on FeNO endpoints.
2.6.2.3 Main analyses: pharmacodynamic analyses	To take into account multiplicity adjustment given the high number of markers tested (adjusted p-values will be provided on top of unadjusted ones)	<u>The following section:</u> No multiplicity procedures will be used as the study is exploratory in nature. <u>was replaced by:</u> In all statistical models performed, non adjusted (ie, nominal) p-values and p-values adjusted to control the false discovery rate (FDR) using the Benjamini-Hochberg procedure at a 10% threshold will be systematically presented in all outputs. The adjustment will be done for each of type of biomarkers (e.g., IHC – Biopsy, ICC – Brushing).
2.6.2.4 Correlation analyses between PD variables at baseline	To include analyses of the correlation between biomarkers at baseline	Correlation analyses have been added
2.6.2.5 Correlation analysis between PD variables at baseline and baseline characteristics	To include analyses of the correlation between biomarkers at baseline and baseline characteristics	Correlation analyses have been added
2.6.2.6 Correlation analysis between change from baseline in PD biomarkers and change from baseline in efficacy data at Week 12/EOT	To include analyses of the correlation between changes in biomarkers and change in efficacy data at Week 12/EOT	Correlation analyses have been added
2.6.2.7 Specific analyses on eosinophil data	To better understand the correlations between change in eosinophil between matrices, and the correlations between changes in eosinophils and change in FeNO	Correlation analyses and descriptive analyses have been added
2.6.2.8 Exploratory predictive/prognostic analyses on change from baseline in efficacy data	To identify prognostic/predictive markers of the response to dupilumab in efficacy data at Week 12/EOT (exploratory analyses)	Exploratory univariate and multivariate prognostic/predictive analyses have been added

<b>SAP section</b>	<b>Rationale</b>	<b>Description of statistical changes</b>
2.7 Analysis of efficacy variables	To describe analyses performed on all efficacy parameters (only analyses on FEV1 was presented in the protocol) ; in addition the specifications of the mixed-effect model with repeated measures used has been corrected to be consistent with EFC13579 study	Statistical analyses on asthma control questionnaire 5-question version score and electronic diary/PEF data have been added, using mixed-effect model with repeated measures
2.8 Analysis of safety data	To harmonize the definition of the safety epochs with EFC13579 study	The treatment-emergent adverse event period will be defined as the time from the first administration of the IMP to the last administration of the IMP + 98 days or until rollover to the OLE study
2.8.1.3 Treatment-emergent adverse events	To describe that treatment-emergent adverse events will be summarized by system organ class and preferred term, and not according to system organ class, high-level group term, high level term and preferred term, due to the low study sample size and study duration	All treatment-emergent adverse events tables will be presented by system organ class and preferred term
2.9.2 Anti-drug antibodies analysis	To take into account the short study duration, no classification of treatment-emergent ADA response will be done	The classification of treatment-emergent ADA response transient, persistent or indeterminate has been removed
2.9.2 Anti-drug antibodies analysis	To include ADA-PD analyses	Association of ADA with main pharmacodynamic endpoints may be explored
2.10 Exploratory pharmacokinetic/pharmacodynamic analysis	To include PK/PD analyses in order to explore the relationship between dupilumab concentrations and selected bronchoscopy parameters	A PK/PD analysis section has been added

## **1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN**

Not applicable

## 2 STATISTICAL AND ANALYTICAL PROCEDURE

### 2.1 PATIENT DESCRIPTION

#### 2.1.1 Disposition of patients

This section describes patient disposition for patient study status.

Screened patients are defined as any patient who signed the informed consent.

Randomized patients consist of all patients with a treatment kit number allocated and recorded in the IVRS/IWRS database, and regardless of whether the treatment kit was used or not.

For patient study status, the total number of patients in each of the following categories will be presented in the Clinical Study Report (CSR) summary table (number and percentage):

- Screened patients.
- Screened failure patients and reasons for screen failure.
- Nonrandomized but treated patients.
- Randomized patients.
- Randomized but not treated patients and reason for not being treated.
- Randomized and treated patients.
- Patient who completed the 12-week treatment period as per protocol.
- Patients who did not complete the 12-week treatment period by main reason for permanent treatment discontinuation.
- Patients who did not complete the 12-week treatment period per patient's decision.
- Patients who completed the study as per protocol.
- Patients who withdraw from the study by main reason for study discontinuation.
- Patients who withdraw from the study per patient's decision.
- Patients who entered the LTS12551 study (OLE).
- Patients who did not continue into the LTS12551 study.
- Patients' status (alive, dead) at last study contact for patients who did not enter the LTS12551 study.

For all categories of patients (except for the screened categories and nonrandomized categories) percentages will be calculated using the number of randomized patients as denominator. This summary will be provided by treatment group and may also be further subgrouped by region and/or ICS dose as applicable.

### 2.1.2 Protocol deviations

During the blinded review of the database, compliance with the protocol will be examined with regard to inclusion and exclusion criteria, prohibited therapies, and timing and availability of planned assessments. Protocol deviations will be identified by the study team before database lock, and classified as minor, major or critical deviations. All critical or major deviations potentially impacting PD, efficacy or PK analyses, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group in the randomization population, and listed.

### 2.1.3 Randomization and drug-dispensing irregularities

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 patient is randomized, b) a patient is randomized based on an incorrect stratum, or c) a patient is randomized twice.  
OR
2. A patient is dispensed an investigational medicinal product (IMP) kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis. The irregularities to be prospectively identified include but are not limited to:

- Kit dispensation without IVRS/IWRS transaction.
- Erroneous kit dispensation at randomization or any post-randomization visit.
- Allocated kit not available.
- Non eligible patient randomized by error.
- Patient randomized twice.
- Stratification error.
- Patient switched to another site.
- Randomisation of a non-existent patient.

All randomization and drug-dispensing irregularities will be documented in the CSR. These irregularities will be categorized, listed and summarized among randomized patients (number and percentages). Nonrandomized but treated patients will be described separately.

In all analyses, in case of stratification error, the real randomization strata (region or ICS dose) will be used instead of the IVRS/IWRS ones.

## **2.2 ANALYSIS POPULATIONS**

The randomized population includes any patient who has been allocated by IVRS/IWRS to a treatment kit regardless of whether the treatment kit was used or not.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

For all analyses (pharmacodynamic, efficacy, safety and ADA), the patients will be analyzed according to the treatment they actually received (“as-treated” analyses). A patient will be included in the dupilumab group if he/she mistakenly received both placebo and dupilumab during the course of the study.

All analysis populations will be summarized in a table by number of patients on the randomized population. All exclusions from any analysis populations will be fully documented in the CSR.

### **2.2.1 Pharmacodynamic populations**

Two PD populations will be defined:

- The bronchoscopy PD population will encompass all randomized and treated patients with an evaluable bronchoscopy performed at baseline and at Week 12/EOT; this population will be used for the analyses of the bronchoscopy PD endpoints;
- The secondary PD population will encompass all randomized and treated patients; this population will be used for the analyses of other PD endpoints.

Patients treated without being randomized will not be included in any PD populations.

### **2.2.2 Efficacy population**

Exploratory efficacy analyses will be performed on the secondary PD population.

### **2.2.3 Safety population**

The safety population will consist of all patients randomized and exposed to IMP, regardless of the amount of treatment administered. Patients treated without being randomized will be included in the safety population. The patients for whom it is unclear whether they took the study medication will be included in the safety population.

### **2.2.4 Pharmacokinetic population**

The PK population will consist of all patients in the safety population with at least one non-missing and eligible post-baseline dupilumab serum concentration data.

## 2.2.5 Pharmacokinetic/pharmacodynamic population

The PK/PD population will consist of all randomized and treated patients with at least one post-baseline PD data and at least one post-baseline dupilumab serum concentration data. Patients will be analyzed according to the treatment actually received. The patients treated with placebo might be included in the PK/PD population depending on the analyses, if they have post-baseline PD data.

## 2.2.6 Anti-drug antibody population

The anti-drug antibody (ADA) population will consist of all patients in the safety population who had at least one non missing ADA result (either “ADA negative” or “ADA positive”) after first dose of the study treatment.

## 2.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

### 2.3.1 Demographic characteristics, medical history, and diagnoses

All analyses will be performed on the randomized population.

#### *Demographic characteristics*

Continuous data will be summarized using the number of available data, mean, SD, median, minimum and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Demographic variables include:

- Age in years (quantitative and qualitative variable :  $\geq 18$ -<40,  $\geq 40$ - $\leq 65$ ).
- Gender (Male, Female).
- Region (North America: Canada and USA; Europe: Germany, UK, Denmark and Sweden).
- Race (Caucasian/White, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other).
- Ethnicity (Hispanic, Not Hispanic).
- Height in cm.
- Weight in kg (quantitative and qualitative variable: <50,  $\geq 50$ -<100 and  $\geq 100$  kg).
- Body mass index (BMI) in kg/ m<sup>2</sup> (quantitative and qualitative variable: <25,  $\geq 25$ -<30,  $\geq 30$  kg/m<sup>2</sup>).
- Alcohol drinking frequency (Never, At least monthly, At least weekly, and At least daily), number of standard alcohol drinks on a typical day when drinking (1 or 2, >2).

The demographic characteristics will be summarized by treatment group separately and overall using descriptive statistics. The summary demographic characteristics will also be provided for other analysis populations or subgroups if there is a noticeable difference in sample size. No statistical testing on demographic characteristics will be performed.

### ***Medical or surgical history***

Medical or surgical history includes all the relevant medical or surgical history during the lifetime of the patient.

The information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

The medical and surgical history will be summarized by treatment group and overall, and by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC based on the overall incidence across treatment groups.

Comorbidity history will be summarized separately. The following comorbid diseases will be summarized:

- Atopic dermatitis history (Yes, Ongoing condition).
- Allergic conjunctivitis history (Yes, Ongoing condition).
- Allergic rhinitis history (Yes, Ongoing condition).
- Allergic conjunctivitis and/or rhinitis history (Yes, Ongoing condition).
- Chronic rhinosinusitis history (Yes, Ongoing condition).
- Nasal polyps history (Yes, Ongoing condition).
- Eosinophilic esophagitis history (Yes, Ongoing condition).
- Food allergy history (Yes, Ongoing condition).
- Hives history (Yes, Ongoing condition).

In addition, a patient will be considered to have ongoing atopic medical condition if he/she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE  $\geq 100$  IU/mL and at least one aeroantigen specific IgE is positive ( $\geq 0.35$  IU/mL) at baseline. Ongoing atopic medical condition will be summarized by treatment group and overall.

### ***Disease characteristics***

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

- ICS dose level (medium, high as defined in [Appendix B](#)).
- Age of asthma onset (quantitative and in classes: <18 years, ≥18-<40, ≥40 years).
- Time since first diagnosis of asthma (years).
- Time since last severe asthma exacerbation (months); a severe asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid burst or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma.
- Number of severe asthma exacerbation experienced within 1 year before Visit 1 (quantitative variable and qualitative variables: 0, 1, 2, 3, ≥4).
- Number of severe asthma exacerbations requiring hospitalization or urgent medical care experienced within 1 year before Visit 1 (quantitative variable and qualitative variables: 0, 1, 2, 3, ≥4).
- Smoking history (Never, Former), time since cessation of smoking (years) and smoking quantity in pack-years for former smokers.
- Baseline spirometry data including pre-bronchodilator Forced Expiratory Volume in One Second (FEV<sub>1</sub>, in L, quantitative and in class: ≤1.75 and >1.75L), percent predicted FEV<sub>1</sub> (%), quantitative and in class: <60% and ≥60%), post bronchodilator FEV<sub>1</sub> (L) and FEV<sub>1</sub> reversibility (%).
- AM and PM Peak Expiratory Flow (PEF) (L/min).
- AM and PM symptom scores.
- Asthma control questionnaire 5-question version (ACQ-5) score (quantitative and in classes : ≤2 and >2).
- Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief in a 24-hr period.
- Hypersensitivity to aspirin or nonsteroidal anti-inflammatory drug (NSAID; Yes, Ongoing condition).
- Blood eosinophils (quantitative and in class: <0.15 and ≥0.15 Giga/L; <0.3 and ≥0.3 Giga/L).
- FeNO in ppb (quantitative and in class: <50 and ≥50 ppb).
- Total IgE in IU/mL.

### 2.3.2 Baseline pharmacodynamics parameters

The baseline PD biomarker parameter is defined as the last non-missing value prior to the first dose of IMP unless otherwise specified (see [Section 2.6.1](#) for more details).

All baseline PD biomarker parameters are presented along with the post-baseline PD biomarker summary statistics by treatment group separately in the PD populations.

No statistical testing on the baseline PD parameters will be performed.

### **2.3.3 Baseline efficacy parameters**

The baseline value of spirometry parameters and ACQ5 score is defined as the last available value up to Week -2 to -0.5 before the bronchoscopy unless otherwise specified.

The baseline AM PEF is the mean of available AM measurements recorded for the 7 days up to Week -2 to -0.5 before bronchoscopy, and the baseline PM PEF is the mean of available PM measurements recorded for the 7 days up to Week -2 to -0.5 before bronchoscopy.

All baseline efficacy parameters are presented along with the post-baseline efficacy parameters summary statistics by treatment group.

No statistical testing on baseline efficacy parameters will be performed.

### **2.3.4 Baseline safety parameters**

The baseline value of safety parameters is defined as the last available value prior to the first dose of IMP. No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

## **2.4 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE**

The extent of study treatment exposure and compliance will be assessed and summarized by actual received treatment within the safety population.

### **2.4.1 Extent of study treatment exposure**

The extent of IMP exposure will be assessed by the duration of IMP exposure. Duration of IMP exposure in days is defined as: last dose date - first dose date + 14 days, regardless of unplanned intermittent discontinuations (see [Section 2.11.5](#) for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum).

### **2.4.2 Compliance**

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations the patient was planned to take during the treatment period (i.e., from the first to the last administration).

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). If needed, the percentage of patients whose compliance is < 80% will be summarized.

## 2.5 PRIOR/CONCOMITANT MEDICATION/THERAPY

All medications taken within 3 months before screening and until the end of the study, including asthma controller medications and systemic corticosteroids, are to be reported in the case report form (CRF) pages.

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

- Prior medications are those the patient used prior to the first IMP injection. Prior medications can be discontinued before the first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first administration of IMP to the last administration of IMP + 98 days or till rollover to the OLE study.
- Post-treatment medications are those the patient took in the period from the last administration of IMP + 99 days to the end of the study.

A given medication can be classified as a prior medication, concomitant medication and post-treatment medication at the same time.

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medication received during the first IMP to the last IMP + 14 days and concomitant medication received during the first IMP to the last IMP + 98 days will be summarized separately. The tables for concomitant medications will be sorted by decreasing frequency of ATC followed

by all other therapeutic classes based on the incidence in the dupilumab group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, following treatments will be summarized separately:

- ICS in combination with other controllers and reliever medications
- Prednisone/prednisolone prescribed post-bronchoscopy

### 2.5.1 ICS in combination with one or two other controllers

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination or concurrently with other controllers as used just prior to screening.

ICS and other asthma controller medications will be identified as the medications reported on the “Prescribed Asthma Controller Medications” eCRF page.

The total daily dose of ICS in asthma controller medication at randomization will be classified as medium-dose or high-dose according to [Appendix B](#). If a patient takes more than one medication containing ICS, the ICS dose of different products will be standardized according to equivalent dose specified in [Table 2](#). The equivalent dose is determined based on the thresholds in [Appendix B](#). After conversion, the total daily dose for inhaled corticosteroid will be calculated and classified as medium or high dose.

**Table 2 – Equivalent dose for inhaled corticosteroids for adults**

Inhaled corticosteroid	Equivalent dose (mcg) to 500 mcg Fluticasone propionate (DPI or HFA)
FLUTICASONE FUROATE	200-*
BECLOMETASONE DIPROPIONATE (CFC)	1000
BECLOMETASONE DIPROPIONATE (HFA)	400
BUDESONIDE (DPI)	800
CICLESONIDE (HFA)	320
MOMETASONE FUROATE	440
TRIAMCINOLONE ACETONIDE	2000

ADAPTED FROM GINA 2016 GUIDELINES

HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler

\*Fluticasone furoate (FF) dose  $\geq$  200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of  $(FF \text{ dose} + 1) \times 2.5$ ; FF dose  $<$ 200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of  $FF \text{ dose} \times 2.5$ .

Example: A patient received 400 mcg budesonide (DPI) and 440 mcg mometasone furoate. They are equivalent to 250 mcg and 500 mcg fluticasone propionate correspondingly. The combined total daily dose is equivalent to 750 mcg fluticasone propionate and classified as high dose.

Number of controllers taken by each patient will be counted by therapeutic drug class. All drugs in a therapeutic class will be only counted once.

## Description of controller medications

Prior asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the overall treatment group.

Concomitant asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in treatment group.

Number and percentage of patients on high-dose ICS, medium-dose ICS, and any non-ICS controller medication, LABA, long-acting muscarinic antagonist (LAMA), and LTRA at baseline will also be summarized.

## Compliance for controller medications

During the study, the daily intake of each prescribed asthma controller medication will be recorded on the electronic diary every evening. Compliance for the controller medications with ICS component and overall compliance to all prescribed controller medications will be calculated for each patient. For each day, a patient is considered as compliant to the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS component is the same as or greater than the prescribed dose. Similarly, a patient is considered as compliant to all controller medication if the actual dose of each controller medication is the same as or greater than the prescribed dose. Following compliances will be calculated and summarized by treatment group:

- **Compliance for controller medication(s) with ICS component** is defined as the number of days when the patient is compliant to the prescribed controller medication(s) with ICS component divided by the number of days the patient stays in the treatment period (from the first dose to the last dose + 14 days).
- **Overall controller medication(s) compliance** is defined as the number of days when the patient is compliant with all prescribed controller medication divided by the number of days the patient stays in the treatment period.

### 2.5.2 Reliever medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use recorded in the electronic diary will be converted to the number of puffs as shown on the [Table 3](#).

**Table 3 - Conversation table for reliever medication: Salbutamol/Albuterol Nebulizer Solution**

<b>Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)</b>	<b>Number of puffs*</b>
2.5	4
5.0	8
7.5	12
10	16

\*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs

Example of salbutamol/albuterol Nebulizer-to-Puff Conversion: Patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total daily = 7.5 mg, i.e., 12 puffs.

**Table 4 - Conversation table for reliever medication: Levosalbutamol/Levalbuterol Nebulizer Solution**

<b>Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)</b>	<b>Number of puffs*</b>
1.25	4
2.5	8
3.75	12
5	16

\*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs

Example of levosalbutamol/levalbuterol Nebulizer-to-Puff Conversion: Patient received 3 levosalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 and 11 AM. Total daily = 3.75 mg, i.e., 12 puffs.

Descriptive statistics on the number of puffs of reliever medications by 24 hours will be provided by treatment group and visit.

## **2.6 ANALYSIS OF PHARMACODYNAMIC VARIABLES**

Pharmacodynamic analyses will be performed on the bronchoscopy or on the secondary PD population, depending on the biomarkers.

All values will be assigned to the theoretical visit; unscheduled visit measurements will be included in the computation of baseline if occurred before the 1<sup>st</sup> IMP, but will not be included in any by-visit summaries or statistical models (only scheduled values will be taken into account).

Only data measured before or on the last IMP date + 14 days (on-treatment period) will be taken into account in all analyses.

## 2.6.1 Description of pharmacodynamic variables

There are three types of biomarkers in the study:

- Biomarkers measured in bronchoscopy samples, assessed in biopsy, bronchoalveolar lavage fluid (BALF), and brushing at baseline and Week 12/EOT
  - Immunohistochemistry (IHC)/immunocytochemistry (ICC) markers.
  - Subepithelial thickness in biopsy samples.
  - Differential cell count in BALF samples.
  - RNA markers.
  - Proteins (in brushing and BALF samples).

Note: depending on feasibility, additional biomarkers might be analyzed.

- Biomarkers measured in blood assessed at baseline, Week 6 and 12/EOT (differential cell count, RNA markers, proteins).
- FeNO measured at baseline, Weeks 6, 8, 10 and 12/EOT.

The [Table 5](#) contains the comprehensive list of the bronchoscopy and blood biomarkers that will be assessed during the study.

The last value before the first IMP will be considered as baseline:

- For bronchoscopy parameters, the baseline is defined as the value at Visit 2 (screening).
- For blood biomarkers, the value at visit 2 is considered as baseline unless not available (eg, insufficient volume); in that case the baseline will be the value determined at Visit 1.
- For FeNO, the baseline is defined as the latest value prior to first dosing.

No imputation of missing values will be performed.

Rules for imputation of values below the LLOQ or above the upper limit of quantification (ULOQ) are detailed in [Section 2.11.2](#).

### 2.6.1.1 Main endpoints

The following inflammatory cells measured in biopsy samples by IHC will be considered as the main markers:

- Eosinophils, based on major basic protein (MBP) positive cells; the hypothesis is that dupilumab will decrease tissue eosinophils in patients with persistent asthma compared to placebo, as it was demonstrated in the R668-PH-17214 study that dupilumab potently blocked house dust mite-induced eosinophil infiltration into the lungs of *Il4ra<sup>hu/hu</sup> Il4<sup>hu/hu</sup>* mice.
- Mast cells: tryptase positive, chymase positive.
- T lymphocytes: CD3 positive.

- T helper cells: CD4 positive.
- Goblet cells: MUC5 positive.
- B cells: CD23 positive.

The main endpoints will be the absolute change from baseline, the percent change from baseline as well as the ratio from baseline at Week 12/EOT for:

- The number of positive inflammatory cells per mm<sup>2</sup>, derived by the biostatistics department, for each marker described above as:

$$\frac{\text{Number of positive inflammatory cells}}{\text{Total area of tissue assessed in mm}^2}$$

- For goblet cells (MUC5 positive) only, the following ratios will be also calculated by the biostatistics department:

- $\frac{\text{Total positive area assessed in mm}^2}{\text{Total area of tissue assessed in mm}^2}$
- $\frac{\text{Number of positive inflammatory cells}}{\text{Total positive area assessed in mm}^2}$

All IHC measurements will be assessed in triplicate; the mean of the 3 values will be used for all statistical analyses. Of note, the previous ratios will be calculated for each replicate first and then the 3 replicates will be averaged (the missing values will not be imputed and the average of the replicates will be calculated whatever the number of non missing values)

### **2.6.1.2 Exploratory endpoints**

#### **2.6.1.2.1 Markers measured by ICC**

The following inflammatory markers measured by ICC in BALF and brushing samples will be considered as exploratory markers:

- Eosinophils: MBP positive cells
- Mast cells: tryptase positive
- Macrophages: CD206 positive, CD68 positive
- B cells: CD23 positive

Exploratory endpoints will be the absolute change from baseline, the percent change from baseline as well as the ratio from baseline at Week 12/EOT for:

- BALF samples: The absolute number of stained cells for each marker described above, expressed in cells by mL of fluid and calculated by the biostatistics department:

$$\frac{\text{Absolute number of stained cells}}{\text{Total recovered volume in mL}}$$

- BALF and brushing samples: The following ratios will be also calculated by the biostatistics department for each cell type:
  - $\frac{\text{Absolute number of stained cells}}{\text{Total number of inflammatory cells}}$
  - $\frac{\text{Number of stained CD206 cells}}{\text{Number of stained CD68 cells}}$ , reflecting M2/M1 macrophages differentiation

#### 2.6.1.2.2 Subepithelial thickness markers

The subepithelial thickness measured in the biopsy will be considered as exploratory markers. The geometric mean of the thickness of basement membrane measured in 3 different locations will be computed by biostatistics department (of note, potential missing values will not be imputed and the average of the thickness will be calculated whatever the number of non-missing values).

Measurements will be assessed in duplicate; the geometric mean across the 3 locations will be calculated first and the arithmetic mean of the 2 replicates will be computed (the missing values will not be imputed and the average will be calculated whatever the number of non-missing values)

The absolute and percent change from baseline at Week 12/EOT for these markers will be considered as exploratory endpoints.

#### 2.6.1.2.3 Differential cell counts

The following markers will be considered as exploratory markers:

- Differential cell counts in BALF: neutrophil, eosinophil, lymphocyte, macrophage, epithelial, and mast cell counts
- Differential cell counts in blood: as part of the standard White Blood Cell differential cell count (see [Section 2.8.2](#)), total white blood cell count, neutrophils, eosinophils, basophils, monocytes and lymphocytes will be analyzed at baseline and Week 12/EOT.

The absolute change from baseline, the percent change from baseline as well as the ratio from baseline at Week 12/EOT for these markers will be considered as exploratory endpoints.

#### 2.6.1.2.4 RNA markers

The effect of dupilumab on the mRNA expression of 29 Th2-related genes (see the list of genes in [Appendix D](#)) after quantitative RT-qPCR will be explored. RNA will be isolated from bronchoscopy in biopsy, BALF and brushing samples at baseline and Week 12/EOT and also in blood at baseline only.

Prior to all statistical analyses, mRNA data will be normalized using a combination of the housekeeping genes B2M and GAPDH if  $C_t$  ranges ( $C_{tmax} - C_{tmin}$  among all study samples) of these 2 genes is  $<4$ . If so, the individual  $\Delta C_t$  will be calculated for each patient and visit as follows:  $\Delta C_t = C_{t,target} - C_{t0}$ , where:

$C_{t0}$  = arithmetic mean of  $C_{(t, 2 \text{ housekeeping genes})}$  for each biopsy specimen

For lung samples, the  $\Delta\Delta C_t$  between Week 12/EOT and baseline as well as fold-change from baseline in gene expression will be calculated for each patient as follows:

- $\Delta\Delta C_t = (C_{t,\text{target}} - C_{t0})_{(\text{Week 12})} - (C_{t,\text{target}} - C_{t0})_{(\text{Baseline})}$
- Fold-change,  $FC = 2^{-\Delta\Delta C_t}$

If  $C_t$  ranges of both housekeeping genes are  $\geq 4$ , alternative normalization algorithms, such as Quantile normalization, will be used.

Note: Please note that the statistical analyses for microarray RNA data (to be assessed from biopsy, BALF, and brushing samples at baseline and Week 12/EOT, and from blood sample at baseline only) will be described in a separate document.

#### 2.6.1.2.5 Proteins

Following proteins will be measured:

- In brushing at baseline and Week 12/EOT: 15-LO1, GPX4, LC3, iNOS, DUOX2, FOXA3. The value of the protein expression will be background-subtracted and normalized to GAPDH by the vendor.
- In BALF at baseline and Week 12/EOT: Periostin, Eotaxin-3, MCP-4, TARC, and the following cytokines: IL-6, IFN- $\gamma$ , TNF- $\alpha$ .

Of note, blood urea nitrogen and BALF urea at the corresponding timepoints will be used to correct the protein levels by the dilution factor, i.e., the concentrations will be multiplied by the following factor:  $\frac{\text{BALF urea}}{\text{Blood urea nitrogen}}$  before analysis.

- In blood at baseline, Weeks 6 and 12/EOT: Periostin, Eotaxin-3, MCP-4, TARC, PARC, ECP, Total IgE and regional specific IgE panels (see [Appendix C](#) for the list of the regional specific IgE panels, assessed at Visit 2 and Week 12/EOT only) and the following cytokines: IL-4, IL-5, IL-6, IL-13, IFN- $\gamma$ , TNF- $\alpha$

The absolute and percent changes from baseline in concentration levels will be analyzed as exploratory endpoints.

#### 2.6.1.3 Additional endpoints

FeNO is planned to be assessed at Visit 1 and 2 (screening), Week 6, Week 8, Week 10, Week 12/EOT, and for patients who do not enter the OLE, at EOS.

FeNO will be analyzed as raw data, absolute and percent change from baseline at each visit. Average FeNO from Week 6 to Week 12/EOT will also be computed for each patient; missing values will not be imputed and the average will be calculated whatever the number of missing data; the corresponding change from baseline will be derived.

If missing interim FeNO values (Week 6, Week 8, or Week 10), the graphical summaries of the missing patterns may be provided to examine if there is any different missing pattern between treatment groups.

The following endpoints will be considered as additional PD endpoints for the study:

- Absolute and percent change from baseline in FeNO at Week 12/EOT
- Absolute change from baseline in the averaged FeNO from Week 6 to Week 12/EOT

No imputation of missing data will be performed.

**Table 5 – Overview of the bronchoscopy and blood biomarkers assessed by matrix, technique and type of biomarkers**

	Bronchoscopy (baseline and Wk 12/EOT)			Blood (baseline, Wk 6, Wk12/EOT)
	Biopsy (6-8 fragments/visit)	Brushing (4-6 samples/visit)	BALF (4 x 50 mL/visit)	
Immuno-histochemistry / Immuno-cytochemistry	Eosinophils (MBP) <sup>a</sup> Mast cells <sup>a</sup> (Tryptase, Chymase) T lymphocytes (CD3) <sup>a</sup> T helper cells (CD4) <sup>a</sup> Goblet cells (MUC5) <sup>a</sup> B cells (CD23) <sup>a</sup>	Eosinophils (MBP) <sup>e</sup> Mast cells <sup>e</sup> (Tryptase) Macrophages <sup>e</sup> (CD206, CD68) B cells (CD23) <sup>e</sup>	Eosinophils (MBP) <sup>e</sup> Mast cells <sup>e</sup> (Tryptase) Macrophages <sup>e</sup> (CD206, CD68) B cells (CD23) <sup>e</sup>	-
Histology/cytology	Subepithelial thickness <sup>b</sup>	-	Differential cell count <sup>c</sup>	Differential cell count <sup>f</sup> (baseline, Wk 12/EOT)
RNA	RT-qPCR panel <sup>g</sup> Microarray <sup>i</sup>	RT-qPCR panel <sup>g</sup> Microarray <sup>i</sup>	RT-qPCR panel <sup>g</sup> Microarray <sup>i</sup>	RT-qPCR panel <sup>g</sup> (baseline only) Microarray (baseline only) <sup>i</sup>
Proteins	-	Th2 panel: 15-LO1, GPX4, LC3, iNOS, DUOX2, FOXA3 <sup>h</sup>	Periostin Eotaxin-3 MCP-4 TARC Cytokines : IL-6, IFN- $\gamma$ , TNF- $\alpha$	Periostin Eotaxin-3 MCP-4 TARC PARC ECP Total IgE and regional specific IgE panels <sup>d</sup> Cytokines : IL-4, IL-5, IL-6, IL-13, IFN- $\gamma$ , TNF- $\alpha$

- a* Following parameters are provided by the lab : total area of tissue assessed, total positive area, number of positive cells; all assessments made in triplicate
- b* Following parameters are provided by the lab: Number of tissue fragments in paraffin-embedded block, total area of tissue measured, total length of epithelium assessed, area of smooth muscle, thickness of basement membrane in 3 locations; all assessments made in triplicate
- c* Following parameters are provided by the lab: Total cell counts as well as neutrophil, eosinophil, lymphocyte, macrophage, epithelial, mast cell counts
- d* See [Appendix C](#) for the list of regional specific IgE panels; assessed at Visit 2 and Week 12/EOT only
- e* Following parameters are provided by the lab: absolute cell number, absolute number of stained cells, total number of inflammatory cells
- f* Part of the standard White Blood Cell differential cell count: total white blood cell count, neutrophils, eosinophils, basophils, monocytes and lymphocytes
- g* See [Appendix D](#) for the panel of Th2-related genes tested
- h* The value of protein expression will be standardized and background-subtracted
- i* Details about  $\mu$ array data as well as their statistical analyses will be provided in a separate statistical analysis plan

## **2.6.2 Description of the analyses**

Bronchoscopy biomarkers will be analyzed on the bronchoscopy PD population and blood biomarkers and FeNO on the secondary PD population.

### **2.6.2.1 Bronchoscopy procedure**

The following numbers and % of patients from the bronchoscopy PD population will be provided by treatment group and by visit:

- Patients with a bronchoscopy performed.
- Patients with a biopsy collected.
- Patients with a biopsy evaluable.
- Patients with a BALF sample collected.
- Patients with a BALF sample evaluable.
- Patients with a brushing sample collected.
- Patients with a brushing sample evaluable.

The location of the biopsy, the BALF sample and the brushing sample (right upper lobe, right middle lobe, right lower lobe, left lower lobe, lingula, left upper lobe) will be also summarized by treatment group and visit.

For the biopsy samples, descriptive statistics (mean, SD, standard error of the mean [SEM], median, Q1, Q3, and range) of the total area of tissue assessed (averaged across the triplicate measurement) will be provided by treatment group and by visit.

### **2.6.2.2 Descriptive statistics**

The descriptive statistics (mean, SD, SEM, median, Q1, Q3, and range) for all biomarkers collected, as well as for the main, exploratory and additional PD endpoints, will be provided by treatment and time point on raw data, absolute changes and percent changes from baseline. The number of imputed values will also be presented when applicable. The descriptive statistics may also be further sub-grouped by region or ICS if need be.

Boxplots will also be provided by treatment and time point. Time profile plots of raw data, absolute and percent change from baseline and ratio from baseline (mean  $\pm$  SEM and/or median with interquartile range) will also be produced by treatment group when applicable.

For each type of inflammatory cell in the biopsy, BALF (measured by ICC or cytology) and brushing samples, the number and % of patients with no positive cell and those with positive cells will be also provided by treatment group and visit. The number and % of patients with no positive cell and those with positive cells at Week 12/EOT will be also provided according to the baseline status (with or without positive cell), by treatment group.

### **Note about allergen-specific IgE measures**

The descriptive statistics for regional specific IgEs at each visits and corresponding plots will be performed only on patients who are sensitized to the specific allergen at baseline using two thresholds:

- Positive baseline result, ie,  $\geq 0.35$  IU/mL.
- Baseline result above the LLOQ, ie,  $\geq 0.1$  IU/mL.

### **2.6.2.3 Main analysis: pharmacodynamic analyses**

The objective of the PD analyses is to compare the post-baseline levels of biomarkers between dupilumab and placebo.

#### **Analysis of the main PD endpoints**

For each inflammatory cell measured in biopsy samples by IHC, a formal statistical modeling will be performed on both absolute change from baseline and ratio from baseline for the number of positive cells/mm<sup>2</sup> as well as for the two other ratios defined on goblet cells:

- The absolute change from baseline will be compared at Week 12/EOT between dupilumab and placebo using a linear fixed-effect model using SAS© Mixed procedure, with treatment, region and ICS dose level as fixed effects, and the baseline value as continuous covariate. The difference between dupilumab and placebo in least square (LS) mean change from baseline, the corresponding two-sided 90% confidence interval (CI), and p-values will be reported.
- The ratio from baseline will be first log-transformed; the log of the ratio will be compared at Week 12/EOT between both treatment groups using a linear fixed effect model using SAS© Mixed procedure, with treatment, region and ICS dose level as fixed effects, and the log of the baseline value as continuous covariate. Estimates and 90% CIs for the geometric mean of the ratio between treatments and p-values will be obtained by computing estimates and 90% CIs for the differences between LS-means within the linear fixed-effect model framework, and then converting to ratios by the antilog transformation.

The analysis of the residuals will be primarily based on plots of studentized residuals. In case of major deviation to the statistical assumptions (normality of the distribution for instance), a rank-based analysis of covariance (rank ANCOVA) model adjusted for baseline, region and ICS dose will be used instead to compare the main PD endpoints between dupilumab and placebo. P-values comparing the treatment groups will be provided. In case of convergence issues and given the low sample size, some fixed effects (e.g., region, ICS dose) might be removed from the model.

No imputation will be performed for missing values.

#### **Analysis of the additional PD endpoints**

The absolute change from baseline in FeNO will be analyzed using a mixed-effect model with repeated measures (MMRM) approach on the secondary PD population. All post-baseline data

until Week 12/EOT will be taken into account. The model will include the fixed categorical effects of treatment group (dupilumab vs placebo), visit and treatment-by-visit interaction, the ICS dose and the region, as well as the continuous fixed covariate of baseline FeNO value and the baseline FeNO-by-visit interaction. This model will be run using SAS<sup>®</sup> Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Kenward-Roger adjustment. The difference between dupilumab and placebo in LS-mean change from baseline at Week 12/EOT, the corresponding two-sided 90% CI, and p-values will be reported from this model.

This model will also provide the difference between dupilumab and placebo in LS-mean change from baseline in average FeNO from 6-12 weeks, using appropriate contrast. The difference in LS mean change from baseline, the corresponding 90% CI and p-values will be reported.

A similar model will be applied to the percent change from baseline in FeNo, and the difference between dupilumab and placebo in LS-mean percent change from baseline at Week 12/EOT, the corresponding two-sided 90% CI, and p-values will be reported from this model.

The analysis of the residuals will be primarily based on plots of studentized residuals. In case of major deviation to the statistical assumptions (normality of the distribution for instance), other approaches might be considered, such as the ANOVA-type or MMRM on transformed data.

If MMRM model fails to achieve convergence due to complexity of model specification, and given the low sample size, some fixed effects (e.g., region, ICS dose level) or interactions might be removed from the model; other covariance structures may be also tested.

No imputation will be performed for missing values.

### **Analysis of the exploratory PD endpoints**

For biomarkers measured only once post-baseline, a linear fixed-effect model or a rank ANCOVA will be performed similarly to the analyses of the main PD endpoints, on the exploratory PD endpoints (absolute change from baseline and ratio from baseline for markers measured by ICC in BALF and brushing samples, and for different cell counts in BALF; absolute and percent change from baseline for the subepithelial thickness and protein levels; change in gene expression).

For biomarkers measured only twice post-baseline (proteins in blood), a MMRM (or other statistical approaches in case of deviations to the model assumptions) will be performed similarly to the analyses of the additional PD endpoints.

### **Multiplicity issues**

In all statistical models performed, unadjusted (ie, nominal) p-values and p-values adjusted to control the false discovery rate (FDR) using the Benjamini-Hochberg procedure (2) at a 10% threshold will be systematically presented in all outputs.

The adjustment will be done separately for each of group of biomarkers:

- IHC markers in biopsy samples.
- ICC markers in BALF samples.
- ICC markers in brushing samples.
- Subepithelial thickness.
- Differential cell counts in BALF.
- Differential cell counts in blood.
- RNA markers in biopsy.
- RNA markers in BALF.
- RNA markers in brushing.
- Proteins in BALF.
- Proteins in brushing.
- Proteins in blood.
- FeNO.

All the p-values coming from the statistical analyses performed on the corresponding PD endpoints (for absolute change from baseline and ratio from baseline, for all types of markers within a group) will be taken into account for the multiplicity adjustment.

#### **2.6.2.4 Correlation analyses between PD variables at baseline**

Following analyses will be performed using all pooled groups.

Spearman's correlation coefficients and the corresponding nominal p-values will be computed between each pair of biomarkers at baseline and presented graphically using a heatmap. In addition, a correlation network (using Cytoscape© software) will be produced in order to represent the interaction between biomarkers. Scatter plots might be produced for selected parameters

Hierarchical clustering (based on Spearman's dissimilarity and Ward aggregation method) will be also performed for each different set of biomarkers (IHC markers in biopsy sample, ICC markers in BALF, etc.) and overall. A heatmap of each correlation matrix and overall will be represented, and based on the clustering, groups of similar biomarkers may be identified.

In particular, these analyses will enable to understand the correlations of eosinophil counts between the 4 matrices (tissue biopsy, BALF, brushings and blood).

### **2.6.2.5 Correlation analysis between PD variables at baseline and baseline characteristics**

Following analyses will be performed using all pooled groups.

Spearman's correlation coefficients between all PD variables at baseline and quantitative baseline characteristics (demographics, disease characteristics in particular spirometry data) and the corresponding nominal p-values will be computed. Bar charts plots of the biomarker value at baseline according to qualitative baseline characteristics (eg, gender, BMI group) may also be generated.

### **2.6.2.6 Correlation analysis between change from baseline in PD biomarkers and change from baseline in efficacy data at Week 12/EOT**

Following analyses will be performed separately by treatment group using the following efficacy parameters (see [Section 2.7](#) for the definition of parameters):

- Change from baseline in pre-bronchodilator FEV<sub>1</sub> and post-BD FEV<sub>1</sub> at Week 12/EOT
- Absolute and percent change from baseline in FeNO at Week 12/EOT

Spearman's correlation coefficients and the corresponding nominal p-values will be computed between absolute and percent change from baseline at Week 12/EOT in all biomarkers and change from baseline in efficacy parameter at the same visit. Scatter plots will also be provided for selected PD parameters.

### **2.6.2.7 Specific analyses on eosinophil data**

Following correlation analyses will be performed separately by treatment group, similar to what is described in [Section 2.6.2.6](#):

- Correlations between absolute change from baseline in eosinophils at Week 12/EOT in tissue biopsy, brushing, BALF and blood samples.
- Correlations between percent change from baseline in eosinophils at Week 12/EOT in tissue biopsy, brushing, BALF and blood samples.

In addition, the following descriptive statistics will be provided, by treatment group and by change in blood eosinophils (>0 or ≤0) at W12/EOT:

- N(%) of patients presenting a >0 or ≤0 change from baseline at W12/EOT in eosinophils in biopsy, brushing and BALF samples.
- Descriptive statistics of change from baseline at W12/EOT in eosinophils in biopsy, brushing and BALF samples.

Following correlations with FeNo will be also performed:

- Correlation between absolute change from baseline in eosinophils at Week 12/EOT in vs the absolute change from baseline in FeNO at the same visit, separately for each matrix (blood, biopsy, brushing and BALF).
- Correlation between percent change from baseline in eosinophils at Week 12/EOT in vs the percent change from baseline in FeNO at the same visit, separately for each matrix (blood, biopsy, brushing and BALF).

### **2.6.2.8 Exploratory predictive/prognostic analyses on change from baseline in efficacy data**

#### **Univariate analyses**

For each biomarker, the prognostic and predictive effects of baseline biomarker on change from baseline in efficacy parameters described in [Section 2.6.2.6](#) at Week 12/EOT will be explored, using a linear fixed effect model, with treatment group, region, ICS dose as fixed effects, baseline biomarker and baseline efficacy parameters as continuous covariates, and baseline biomarker-by-treatment group interaction; unadjusted p-values for the baseline biomarker effect (prognostic effect) as well as the for the interaction (predictive effect) will be reported; adjusted p-values for FDR will be also presented (the adjustment will be done for each of type of biomarkers). The biomarkers that will be considered are the main and exploratory PD endpoints.

In case of convergence issues and given the low sample size, some fixed effects (e.g., region, ICS dose) might be removed from the model.

Similar analyses may be performed using binary expression of the biomarker at baseline (high vs low according to LLN or  $<$  vs  $\geq$  median overall groups).

#### **Multivariate analyses**

If some biomarkers show up to be potentially prognostic/predictive in the previous univariate analyses (using change from baseline in efficacy parameters as defined in [Section 2.6.2.6](#)), exploratory multivariate analyses will be performed in order to identify predictive biomarkers and subgroups of patients with enhanced treatment effect. Following analyses may be conducted:

- Linear regressions with baseline levels of several biomarkers as covariates.
- Linear regression with the combination of 2 biomarkers defined as binary criteria as covariate.

A proper cross-validation scheme including the univariate selection step will be put in place to estimate the generalization error of the model.

## **2.7 ANALYSIS OF EFFICACY VARIABLES**

### **2.7.1 Parameters**

All efficacy parameters are exploratory and include:

- Disease-specific efficacy measures: spirometry, asthma control questionnaire 5-question version (ACQ5) score.
- Disease-specific, daily efficacy assessment.

### **2.7.1.1 Disease-specific efficacy measures**

#### **Spirometry**

Spirometry will be done in accordance with meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines at screening, Week 2, 4, 6, 8, and 12/EOT, and for patients who do not rollover to the OLE study, Week 14, 18 and 24/EOS. Details about spirometry testing procedure are provided in protocol (section 9.3.1.1).

The exploratory endpoints for spirometry are the following ones:

- Absolute change from baseline in pre-BD FEV<sub>1</sub> at Weeks 2, 4, 6, 8 and 12/EOT,
- Percent change from baseline in pre-BD FEV<sub>1</sub> at Weeks 2, 4, 6, 8 and 12/ EOT,
- Absolute change from baseline in other lung function measurements (post-BD FEV<sub>1</sub>, % predicted FEV<sub>1</sub>, forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%) at Weeks 2, 4, 6, 8 and 12/EOT.

#### **ACQ-5**

The ACQ-5 was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. The ACQ-5 has 5 questions, reflecting the top-scoring five asthma symptoms: woken at night by symptoms, wake in the mornings with symptoms, limitation of daily activities, shortness of breath and wheeze. Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment; see [Appendix E](#)).

A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ (3), 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 imputed (pro-rated) using the completed questionnaires from the previous visit. For instance, answer to question 5 is missing at Visit 2, and all questions are completed at Visit 1. Then the question 5 score at Visit 2 is imputed as: (sum of score at Visit 2/sum of scores excluding question 5 at Visit 1) × score of question 5 at Visit 1. 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.

The exploratory endpoints for ACQ5 are the following ones:

- Absolute change from baseline in ACQ5 score at Weeks 4, 8, 12/EOT, 16 and EOS.

### **2.7.1.2 Disease-specific, daily efficacy assessment**

On a daily basis throughout the study, the patient uses an electronic diary / PEF meter to:

- Measure morning and evening PEF,
- Indicate the number of inhalations/day of salbutamol/albuterol or, levosalbutamol/levalbuterol for symptom relief,
- Record the number of inhalations/day of background product used,
- Record oral steroids use after bronchoscopy and for exacerbation event.

At screening (Visit 1), patients will be issued an electronic diary/PEF. Patients will be instructed on the use of the device, and written instructions on the use of the electronic PEF meter will be provided to the patients. In addition, the investigator will instruct the patients on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 12:00 PM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol,
- PM PEF performed in the evening (between 5:30 PM and 12:00 AM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol,
- Patients should try to withhold albuterol/salbutamol or levalbuterol/levosalbutamol for at least 6 hours prior to measuring their PEF,
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation.

Baseline AM PEF will be the mean AM measurement recorded for the 7 days prior to Visit 2, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to Visit 2. There should be at least 4 days' measurement out of the 7 days for setting up the period stability limit/baseline, and the first dosing visit should be rescheduled until data for 4 days are available. In case less than 4 days' measurement is available during the 7 days prior to randomization, the baseline AM/PM PEF is the mean of the 4 AM/PM PEF prior to and closest to randomization during the whole screening period. For the daily measurements, calculation of periodical average specified in [Section 2.11.3](#) will be implemented.

Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2.

The exploratory endpoints for AM/PM PEF are the following ones:

- Absolute change from baseline in morning [AM]/evening [PM] peak expiratory flow [PEF] at Weeks 2, 4, 6, 8 and 12.

## 2.7.2 Analyses

The change from baseline in efficacy parameters will be analyzed using a MMRM approach based on the secondary PD population. All on-treatment data until Week 12/EOT will be taken into account, i.e., data measured before or on the last IMP date + 14 days. The model will include the fixed categorical effects of treatment group (dupilumab vs placebo), visit and treatment-by-visit interaction, the ICS dose level and the region, as well as the continuous fixed covariate of baseline efficacy endpoint and the baseline-by-visit interaction. This model will be run using SAS© Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Kenward-Roger adjustment. The between-group difference (dupilumab vs placebo) in LS-mean change from baseline at each visit the corresponding two-sided 90% CI, and p-values will be reported from this model.

If MMRM model fails to achieve convergence due to complexity of model specification, and given the low sample size, some fixed effects or interactions might be removed from the model; other covariance structures may be also tested.

No imputation will be performed for the MMRM model.

## 2.8 ANALYSIS OF SAFETY DATA

All safety analyses will be performed on the safety population, unless otherwise specified.

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG and physical examination.

All safety endpoints are considered as additional endpoints in this study.

### *Observation period*

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the time prior to the first administration of the IMP.
- The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of the IMP + 14 days or until rollover to the OLE study.
- The **residual treatment** epoch is defined as the time from the last administration of the IMP + 15 days to the last administration of the IMP + 98 days or until rollover to the OLE study.
- The **posttreatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the end of the study (defined as last

protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events of special interest).

The treatment-emergent adverse event (TEAE) period will include both treatment and residual treatment periods.

The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or lost to follow-up or the resolution/stabilization of all serious adverse events and adverse events of special interest).

The summary of safety results will be presented by treatment group.

### ***General common rules***

- The baseline value is defined as the last available value before the first dose of IMP.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- All safety values will be assigned to the theoretical visit; unscheduled visit measurements will be included in the computation of baseline if occurred before the 1<sup>st</sup> IMP and will be taken into account in the PCSAs analyses, but will not be included in any by-visit summaries or statistical models (only scheduled values will be taken into account).

### ***General common rules related to PCSA for clinical laboratory evaluations, vital signs, and ECG***

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG ([Appendix F](#)).
- PCSA criteria will determine which patients has at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population. Number (%) of patients with at least 1 PCSA will be summarized regardless of baseline PCSA status and also by baseline PCSA status.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group.

## 2.8.1 Analysis of adverse events

### 2.8.1.1 Definitions

Adverse event observation period:

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to the first administration of IMP.
- TEAEs are adverse events that developed or worsened or became serious during the TEAE period.
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period.

All AEs (including serious adverse events and adverse events of special interests) will be coded with a lower-level term (LLT), PT, high-level term (HLT), high-level group term (HLGT), and associated primary SOC using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Adverse events of special interest (AESI) and other selected AE groupings will be searched based on the criteria detailed in [Table 6](#).

**Table 6 - Criteria for adverse events of special interest and other selected AE groupings**

<b>AE Grouping</b>	<b>Criteria</b>
<b>AESI</b>	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach ( <i>Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1</i> ): includes anaphylactic reaction narrow SMQ (20000021) terms; for selection based on occurrence of multiple events, the events must have occurred within 24 hours of each other
Hypersensitivity (medically reviewed)	SMQ hypersensitivity (20000214) narrow search and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant events
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥ 24 hours or ongoing
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status
Parasitic infection	Infection Type 'Parasitic' checked on eCRF Infection Defined as AESI Complementary Form
Opportunistic infection	Infection Type 'Opportunistic' checked on eCRF Infection Defined as AESI Complementary Form
Drug-related hepatic disorder	Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006)
Pregnancy	Primary SOC = 'Pregnancy, puerperium and perinatal conditions' or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination)
Symptomatic overdose with IMP	Is the event a Symptomatic Overdose with IMP? is answered Yes on AE eCRF.
Symptomatic overdose with non-IMP	Is the event a Symptomatic Overdose with non-IMP? is answered Yes on AE eCRF
<b>Other selected AE grouping</b>	
Injection site reaction	HLT = 'Injection site reaction'
Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors
Suicidal behavior	PT in (Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt)
Partner pregnancy	PT in (Pregnancy of partner, Miscarriage of partner)
Conjunctivitis (narrow)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis)
Conjunctivitis (broad)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia)
Eosinophilia	HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'

### **2.8.1.2 General information**

The primary focus of adverse event reporting will be on TEAEs. Pretreatment adverse events will be described separately.

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 pretreatment or treatment-emergent. 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 pretreatment. Details on classification of adverse events with missing or partial onset dates are provided in [Section 2.11.5](#).

Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Sorting will be based on results for the dupilumab group.

### **2.8.1.3 Treatment-emergent adverse events**

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - Treatment-emergent adverse event.
  - Serious treatment-emergent adverse event.
  - Treatment-emergent adverse event leading to death.
  - Treatment-emergent adverse event leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, showing number (%) of patients with at least 1 TEAE, sorted by internationally agreed order of primary SOC.
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT.
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All TEAEs by maximal intensity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE by severity (i.e., mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All TEAEs regardless of relationship and related to IMP by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- A listing of all treatment-emergent adverse events will be presented.

#### **2.8.1.4 Treatment-emergent adverse event(s) leading to permanent treatment discontinuation or drug interruption**

A listing of all treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption will be presented

#### **2.8.1.5 Adverse events of special interests and other selected AE groupings**

- All AESIs by selected standardized MedDRA query (SMQ) and PT or by laboratory values (as in ALT elevation), showing the number (%) of patients with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ
- For each pre-specified AESI and selected AE grouping,
  - Number (%) of patients with any specific TEAE.
  - Number (%) of patients with any specific serious AE (regardless of treatment emergent status).
  - Number (%) of patients with any specific treatment emergent serious AE.
  - Number (%) of patients with any specific AE leading to death.
  - Number (%) of patients with any specific TEAE leading to permanent study drug discontinuation.
  - Number (%) of patients with any specific TEAE by maximum intensity, corrective treatment, and final outcome.
  - Number (%) of patients with any specific TEAE regardless of relationship and related to IMP.
  - All of the specific TEAE, by PT, showing the number (%) of patients, sorted by decreasing incidence of PT.
- Number (%) of patients with injection site reactions by the related injection.
- Number (%) of patients with different numbers of injection site reactions.
- A listing of the AEs will be presented.

#### **2.8.1.6 Death and treatment-emergent serious adverse event(s)**

A listing of all deaths (whatever the period: on-study, on-treatment and poststudy) and a listing of all treatment-emergent serious adverse events (SAE) will be presented.

#### **2.8.1.7 Pretreatment adverse events**

A listing of all pretreatment adverse events will be provided.

### **2.8.2 Clinical laboratory evaluations**

#### **Parameters**

The clinical laboratory data consists of blood analysis, including hematology, clinical chemistry serology, and urinalysis. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at both screening visits, Week 4, Week 8, Week 10 (selected parameters, see below), Week 12/EOT, and for patients who do not enter the OLE, at Week 16 and EOS.

The laboratory parameters will be classified as follows:

- Hematology
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, platelet count, prothrombin time, partial thromboplastin time (PTT) at Visit 1 only.
  - White blood cells: total white blood cell count with five-part differential count (neutrophils, eosinophils, basophils, monocytes and lymphocytes), and total red blood cell count.
- Clinical chemistry
  - Metabolism: glucose, total cholesterol, total protein, creatine phosphokinase.
  - Electrolytes: sodium, potassium, chloride, bicarbonate.
  - Renal function: creatinine, blood urea nitrogen, uric acid.
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), albumin.
  - Anti-nuclear antibody (ANA) at Visit 1 for all patients and at Week 10 only for patients who plans to enter the OLE.
  - Anti-ds DNA antibody will be tested if ANA is positive ( $\geq 1:160$  titer).
  - Pregnancy test: serum  $\beta$ -human chorionic gonadotropin will be performed at screening (Visit 1) in women of childbearing potential.
  - Hepatitis and HIV screen: At Visit 1 (screening) and at Week 10 only for patients planned to enter the OLE). Screen includes: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb [total and IgM]) and hepatitis C virus antibodies (HCV Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies). Patients who are Total-HBcAb positive and HBsAg negative at Visit 1 must undergo HBV DNA testing prior to randomization to determine eligibility. In case of results showing HCV Ab positive, HCV RNA testing must be performed prior to randomization to determine eligibility. At Visit 8, the follow-up testing noted above (HBV DNA or HCV RNA) must be done as needed to determine eligibility for the OLE study.

Urine samples will be collected as follows:

- Urinalysis: Performed at both screening visits, Week 12/EOT, and for patients who do not enter the OLE, EOS. Urine dipstick analysis includes specific gravity, pH, glucose,

ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin. A quantitative measurement for glucose, protein, erythrocytes, and leucocytes will be performed in the event that the urine dipstick is positive for any of the above parameters. If the urine dipstick is positive for proteins, a microscopic analysis will be performed.

- A urine dipstick pregnancy test will be performed at Day 1 prior to randomization, Week 4, Week 8, optional Visit 8.1 (Week 12), Week 12/EOT, Week 16, and EOS.

## **Analyses**

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline and each post-baseline time point) by treatment group. For eosinophils and liver function tests (AST, ALT, alkaline phosphatase, and total bilirubin), mean changes from baseline with the corresponding SEM will be plotted over time in each treatment group. This section will be organized by biological function as specified above.

The incidence of PCSAs (list provided in [Appendix F](#)) at any time during the TEAE period will be summarized by biological function and by treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

A listing of PCSAs will be provided.

### ***Drug-induced liver injury***

If there is any imbalance in the incidence of liver-related adverse events across the treatment groups, analysis of liver-related adverse events will be performed.

The liver function tests (LFT), namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any post baseline visit may be displayed by duration of exposure for each treatment group.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT > 3 x ULN, and associated with an increase in bilirubin  $\geq 2$  x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and creatine phosphokinase, serum creatinine, complete blood count, HCV RNA.

The normalization by parameter (to  $\leq 1$  x ULN or return to baseline) of elevated liver function tests will be summarized by categories of elevation (> 3 x, 5 x, 10 x, 20 x ULN for ALT and AST, > 1.5 x ULN for alkaline phosphatase, and > 1.5 x and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized despite treatment continuation of IMP, or normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category.

### ***Change in Blood Eosinophil***

Mean ( $\pm$  SEM) and median (with the interquartile range) changes from baseline in eosinophil with the corresponding standard error will be plotted over time in each treatment group for patients with baseline blood eosinophil < 0.5 Giga/L and patients with baseline blood eosinophil  $\geq 0.5$  Giga/L.

Number (%) of patients with post-baseline peak blood eosinophil  $\geq 1$  Giga/L,  $\geq 3$  Giga/L and  $\geq 5$  Giga/L will also be summarized in each treatment group and by baseline blood eosinophil status (All, < 0.5 Giga/L,  $\geq 0.5$  Giga/L). A similar table will be produced using the following thresholds  $\geq 0.5$  Giga/L,  $\geq 1$  Giga/L,  $\geq 3$  Giga/L and  $\geq 5$  Giga/L for baseline and post-baseline assessments.

A summary of number (%) of patients with maximum change from baseline in blood eosinophil  $\leq 0.5$  Giga/L, > 0.5 -  $\leq 1$  Giga/L or > 1 Giga/L will also be provided by treatment group and by baseline blood eosinophil level ( $\leq 0.5$  Giga/L, > 0.5 -  $\leq 1$  Giga/L, > 1 Giga/L).

### **2.8.3 Vital signs**

Vital signs include the systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute) and body temperature (degree Celsius), and will be assessed at all scheduled visits except Week 18. Body weight (kg) will be measured at the first screening visit, Day 1, Week 12/EOT and EOS.

The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of all vital signs variables (raw data and changes from baseline) will be calculated for each visit or study assessment (baseline and each post-baseline time point) by treatment group. For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at the same time points) in each treatment group.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing.

- Abnormal according to PCSA criterion or criteria.

A listing of PCSAs will be provided.

#### **2.8.4 Oxygen saturation**

Oxygen saturation (%) will be measured by pulse oximetry before the bronchoscopy procedure (ie, at the second visit of screening and Week 12/EOT) to ensure patient suitability.

The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) for raw data and changes from baseline will be calculated for each visit by treatment group.

#### **2.8.5 Electrocardiogram**

##### **Quantitative parameters**

A single standard 12-lead ECG will be performed at Screening, Day 1 and Week 12/EOT, and centrally read by an ECG core lab. The following parameters will be received from the ECG core lab and will be analyzed: RR interval (msec), HR (beats/min), PR interval (msec), QRS interval (msec), QT interval (msec), heart-rate corrected QT interval (msec) using Bazett's (QTcB) and Fridericia's formula (QTcF), and QRS axis (degrees).

The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of all quantitative ECG variables (raw data and absolute changes from baseline), except RR interval, will be calculated for each visit or study assessment (baseline, each post-baseline time point) by treatment group.

The incidence of PCSAs at any time during the TEAE period will be summarized by treatment group irrespective of the baseline and/or according to the following baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

A listing of PCSAs will be provided. A separate listing of patients with QTcB/QTcF >480 ms and/or change from baseline in QTcB/QTcF >60 ms will also be provided, using all post-dose timepoints.

##### **Qualitative ECG findings**

The incidence of qualitative findings by the ECG core lab will be summarized by treatment group, separately for ECGs done prior the first dosing and for ECGs done after, for all assessments done during the TEAE period. These findings will include:

- The overall ECG conclusion (Normal ECG; Abnormal ECG, clinically insignificant; Abnormal ECG, potentially clinically significant; ECG unable to evaluate; ECG unable to evaluate but measurements provided are correct).

- All findings sorted by category of finding (rhythm, supraventricular arrhythmias, ventricular arrhythmias, AV conduction, intraventricular conduction, axis and voltage, chamber hypertrophy and enlargement, ST-T abnormalities, ischemia and infarction, technical statements) and finding (refer to the ECG manual for further details about the findings).

## 2.9 ANALYSIS OF PHARMACOKINETIC DATA

All endpoints in this section are considered as additional endpoints in the study.

### 2.9.1 Dupilumab concentration analysis in serum

Concentrations of dupilumab in serum will be measured at Day 1 predose, Week 2, Week 6, Week 8, Week 12/EOT, and for patients who do not enter the OLE, at Week 18 and EOS.

Concentration will be summarized in the PK population using arithmetic and geometric means, SD, SEM, coefficient of variation (CV), minimum, median and maximum per sampling time. Values will be expressed in the tables with no more than three significant figures. Mean concentrations with the corresponding standard error will be plotted over time.

See data handling conventions for PK variables in [Section 2.11.4](#).

### 2.9.2 Anti-drug antibodies analysis

#### ADA status

Anti-dupilumab antibody status (negative or titer value, if positive in the ADA assay) will be assessed at Day 1, Week 12/EOT, and, for patients who do not enter the OLE, at EOS.

Status in the ADA assay will be classified as the following:

1. Pre-existing immunoreactivity is defined as:

An ADA positive response in the assay at baseline with all post treatment ADA results negative

OR

An ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.

2. Treatment-emergent response is defined as an ADA positive response in the assay post first dose, when baseline results are negative or missing.
3. Treatment-boosted response is defined as an ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

### **Titer values (titer value category)**

- Low (Titer < 1000).
- Moderate ( $1000 \leq \text{Titer} \leq 10000$ ).
- High (Titer > 10000).

ADA positive samples will be further characterized for presence of neutralizing antibody (NAb) response in the NAb assay.

### **ADA status summary**

The following summary will be provided based on the ADA population:

- Number (%) of patients with pre-existing immunoreactivity.
- Number (%) of patients with treatment-emergent ADA.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA.
- Number (%) of patients with treatment-boosted ADA.
- For patients with treatment-boosted ADA:
  - The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer.
  - The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of the ratio of peak post-baseline titer to baseline titer.
- Number (%) of patients with NAb status
- Listing of ADA peak titer levels and NAb status

### **Kinetics of treatment-emergent ADA response**

Number (%) of patients with treatment-emergent ADA response at each visit will be summarized by each treatment group.

Plot of percentage of patients with treatment-emergent ADA response at each visit will be provided by each treatment group.

### **Association of ADA with PD endpoints**

Associations between ADA variables and main PD endpoints may be explored if needed.

## 2.10 EXPLORATORY PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The PK/PD analysis will be done on the PK/PD population as defined in [Section 2.2.5](#). The relationship between dupilumab concentration and selected bronchoscopy biomarkers will be explored through scatter plots. A statistical modeling will be performed if relevant.

## 2.11 DATA HANDLING CONVENTIONS

### 2.11.1 General conventions

The following formulas will be used for computation of parameters.

#### *Demographic formulas*

Age is calculated as:

$$\text{Integer part of (informed consent date – birth date)/365.25}$$

Age of onset of asthma is calculated as:

$$\text{Integer part of (asthma onset date – birth date)/365.25}$$

Due to the Germany regulation, German patients provide the January 1<sup>st</sup> of birth year, instead of standard date birth. The first date of the birth quarter will be used as birth date approximately.

Time since first diagnosis of asthma (years) is calculated as:

$$\begin{aligned} & (\text{Year of randomization – Year of first diagnosis of asthma}) + \\ & (\text{Month of randomization – month of first diagnosis of asthma})/12 \end{aligned}$$

Time since cessation of smoking (month) is calculated as:

$$(\text{Year of randomization – Year of cessation}) \times 12 + (\text{month of randomization – month of cessation})$$

Time since last asthma exacerbation (months) is calculated as:

$$\begin{aligned} & (\text{Year of randomization – Year of last asthma exacerbation}) \times 12 + \\ & (\text{Month of randomization – Month of last asthma exacerbation}) \end{aligned}$$

BMI is calculated as:  $\text{Weight in kg/ (height in meters)}^2$

Smoking quantity (pack-year) is calculated as following:

$$\text{Number of pack-year} = (\text{packs smoked per day}) \times (\text{years as a smoker}) \times 365.25$$

#### *Renal function formulas*

For patients  $\geq 18$  years old, creatinine clearance (CLcr) value will be derived using the equation of Cockcroft and Gault:

$$\text{CLcr (ml/min)} = (140 - \text{age}) \times \text{weight (kg)} \times (1 - 0.15 \times \text{sex (0-M, 1-F)}) / (0.814 \times \text{creatinine } (\mu\text{mol/l}))$$

CLcr will be calculated using the last weight measurement on or before the visit of the creatinine measurement and age at the lab sampling date. Here age is calculated as following:

$$\text{Age} = \text{integer part of } (\text{lab sampling date} - \text{birth date})/365.25$$

### 2.11.2 Data handling conventions for PD biomarkers

For biomarkers with nonnumeric values, the imputed values used for the descriptive statistics will be determined by considering the following rules:

- If database value is < LLOQ, the value used will be LLOQ/2
- If database value is > ULOQ, the value used will be the ULOQ

### 2.11.3 Data handling conventions for efficacy variables

#### *Calculation of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day*

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations per day is the sum of number of inhalations recorded in one diary day including the evening diary and the following day's morning diary.

#### *Periodical average of daily efficacy endpoints at designated study days*

For the daily efficacy endpoints, the time period used to calculate the periodical average at each designated study day is summarized in [Table 7](#). Randomization day is used as the reference day (Day 1).

**Table 7 - Periodical average of daily efficacy assessment**

Time point	Morning PEF, asthma symptom score	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Day 15	2-15	1-14	Diary day 1-14
Day 29	16-29	15-28	Diary day 15-28
Day 43	30-43	29-42	Diary day 29-42
Day 57	44-57	43-56	Diary day 43-56
Day 71	58-71	57-70	Diary day 57-70
Day 85	72-85	71-84	Diary day 71-84
Day 99	86-99	85-98	Diary day 85-98
Day 113	100-113	99-112	Diary day 85-112
Day 127	114-127	113-126	Diary day 113-126

Time point	Morning PEF, asthma symptom score	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Day 141	128-141	127-140	Diary day 127-140
Day 169	142-169	141-168	Diary day 141-168
Day 183	170-183	169-182	Diary day 169-182
Day 197	184-197	183-196	Diary day 183-196

Note: A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. For example, diary day 14 includes the evening diary on day 14 and the morning diary on day 15.

#### 2.11.4 Data handling conventions for pharmacokinetic variables

If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. For drug-treated patients, where concentration values are below the LLOQ, LLOQ/2 will be used. Values will be expressed in the tables with no more than three significant figures. For patients in the placebo group, concentration values are below the LLOQ will be taken into account with a serum concentration considered equal to 0.

#### 2.11.5 Missing data

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

##### *Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing*

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the Investigational Product Administration report form page. If this date is missing, the exposure duration should be left as missing.

The last dose injection should be clearly identified in the case report form and should not be approximated by the last returned package date.

##### *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 and concomitant medication.

##### *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/time information does not indicate that the adverse event started prior to

treatment or after the treatment-emergent adverse event 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.

***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 injection should be clearly identified in the case report form and should not be approximated by the last returned package date.

***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 possibly related adverse events, but no imputation should be done at the data level.

***Handling of missing severity of adverse events***

If the severity 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.

***Handling of potentially clinically significant abnormalities***

If a patient has a missing baseline, he/she will be grouped in the category “normal/missing at baseline.”

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.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g., for blood eosinophils the PCSA is  $>0.5$  Giga/L or  $>ULN$  if  $ULN \geq 0.5$  Giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

***Handling of missing date/time for PK analyses***

If date and/or time of the drug injection and/or sampling are missing then the concentration will not be taken into account.

### **2.11.6 Statistical technical issues**

None.

### **3 INTERIM ANALYSIS**

No interim analysis is planned.

## **4 SOFTWARE DOCUMENTATION**

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.  
Correlation network will be created using Cytoscape© version 3.6.0 or higher.

## 5 REFERENCES

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3. Juniper E. Asthma control questionnaire: Background, administration and analysis. 2012; QOL Technologies, West Sussex, UK