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STATISTICAL ANALYSIS PLAN

A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-5:	Asthma Control Questionnaire 5-question version
ACQ-7:	Asthma Control Questionnaire 7-question version
ADA:	Anti-drug antibody
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
ALT:	Alanine Aminotransferase
ANA:	Antinuclear Antibodies
AQLQ(S):	Asthma Quality Of Life Questionnaire with Standardized Activities
ATS:	American Thoracic Society
CI:	Confidence Interval
CRF:	Case Report Form
CV:	Coefficient of Variation
DNA:	Deoxyribonucleic acid
DPI:	Dry Powder Inhaler
ECG:	Electrocardiography
ECP:	Eosinophil Cationic Protein
eCRF:	electronic Case Report Form
EOT:	End of Treatment
EQ-5D-5L:	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
ERS:	European Respiratory Society
FeF:	Forced Expiratory Flow
FeNO:	Fractional Exhaled Nitric Oxide
FEV1:	Forced Expiratory Volume in One Second
FVC:	Forced Vital Capacity
GINA:	Global Initiative for Asthma
HADS:	Hospital Anxiety and Depression Scale
HADS-A:	Hospital Anxiety and Depression Scale- Anxiety subscale
HADS-D:	Hospital Anxiety and Depression Scale- Depression subscale
HBc Ab:	Hepatitis B Core Antibody
HBs Ab:	Hepatitis B Surface antibody
HBs Ag:	Hepatitis B Surface Antigen
HBV:	Hepatitis B Virus
HCV:	Hepatitis C Virus
HCV Ab:	Hepatitis C Virus Antibody
HFA:	Hydrofluoroalkane
HIV:	Human Immunodeficiency Virus
HLGT:	High-Level Group Term
HLT:	High Level Term
HRQoL:	Health related quality of life

ICS:	Inhaled Corticosteroid
IgA:	Immunoglobulin A
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
IMP:	Investigational Medicinal Product
IRT:	Interactive Response Technologies
ITT:	Intent-To-Treat
IVRS/IWRS:	Interactive Voice Response System/Interactive Web Response System
K-M:	Kaplan-Meier
LABA:	Long-Acting Beta Agonist
LAMA:	Long-Acting Muscarinic Antagonist
LLQ:	Lower Limit of Quantitation
LLT:	Lower-Level Term
LOAC:	Loss Of Asthma Control
LTRA:	Leukotriene Receptor Antagonist
MCID:	Minimal Clinically Important Difference
MDI:	Metered Dose Inhaler
MedDRA:	Medical Dictionary for Regulatory Activities
MID:	Minimal Important Difference
MMRM:	Mixed-effect Model with Repeated Measures
NRS:	Numerical Rating Scale
NSAID:	Nonsteroidal Anti-inflammatory Drug
OLE:	Open Label Extension
PCSA:	Potentially Clinically Significant Abnormalities
PEF:	Peak Expiratory Flow
PK:	Pharmacokinetics
Post-BD:	Post-bronchodilator
Pre-BD:	Pre-bronchodilator
PROs:	Patient-Reported Outcomes
PT:	Preferred Term
RBC:	Red Blood Cell
RNA:	Ribonucleic Acid
RQLQ(S)+12:	Standardized Rhinoconjunctivitis Quality Of Life Questionnaire , ages 12+
SC:	subcutaneously
SD:	Standard Deviation
SEM:	Standard Error of the Mean
SNOT-22:	22-item Sino Nasal Outcome Test
SOC:	System Organ Class
TARC:	Thymus and Activation-Regulated Chemokine
TEAE:	Treatment-Emergent Adverse Event
ULN:	Upper Limit of Normal
VAS:	Visual Analogue Scale
WBC:	White Blood Cell

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

EFC13579 is a multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma. Both the patient and investigator will be blinded to assigned active drug or matching placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

After a screening phase of 4±1 weeks, patients will be centrally randomized using permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 2:2:1:1 randomization ratio to dupilumab 300 mg q2w in 2mL, dupilumab 200 mg q2w in 1.14 mL, placebo q2w in 2 mL or placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, ≥18 years) at screening, blood eosinophil count (<0.3 Giga/L, ≥0.3 Giga/L) done at the central laboratory at screening, ICS dose level (medium, high) and country.

At least 1638 patients, including approximately 84 adolescent patients, will be randomized to dupilumab or placebo, with at least 690 patients with a baseline blood eosinophil count ≥0.3 Giga/L. Recruitment for patients on medium dose of ICS will be stopped at approximately 819 to ensure at least 50% patients are on high dose of ICS.

1.2 OBJECTIVES

1.2.1 Primary objectives

- To evaluate the efficacy of dupilumab in patients with persistent asthma.

1.2.2 Secondary objectives

- To evaluate the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab on improving PROs including HRQoL
- To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies

1.2.3 Exploratory objectives

- To explore the association of biomarkers with treatment response
- To explore the association of genetic profiles with treatment response
- To explore the association of vaccine response with treatment

1.3 DETERMINATION OF SAMPLE SIZE

The sample size was calculated on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe asthma exacerbations during the 52-week treatment period, and absolute change from baseline in FEV1(L) at Week 12. Assuming the number of severe asthma exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe asthma exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline blood eosinophil count ≥0.3 Giga/L, approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for this subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients (546 for each dupilumab dose and 273 for each matching placebo group) will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12 for the overall population, and 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline blood eosinophil count ≥0.3 Giga/L. The overall study recruitment will continue until at least 1638 patients in total and 690 patients with blood eosinophils ≥0.3 Giga/L are randomized. The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized into the study. In addition, approximately 84 adolescent patients will be randomized.

In addition to the originally planned sample size of 1638 patients, approximately 220 patients will be randomized in order to have additional patients treated with the drug product manufactured using the intended commercial process.

1.4 STUDY PLAN

The clinical trial consists of three periods:

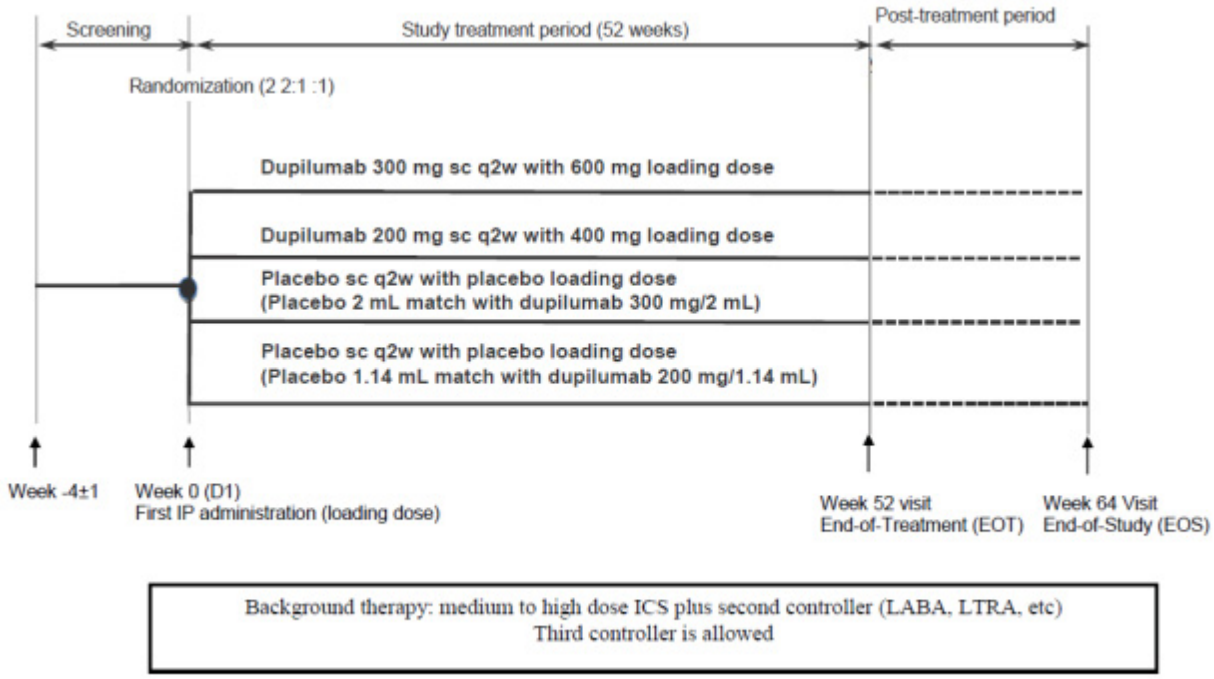
Screening Period (4±1 weeks): to determine a patient's eligibility status and establish level of asthma control before randomization.

Treatment Period (52 weeks): treat with dupilumab or placebo SC injection.

Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the long term extension study.

1.4.1 Graphic study design

Please refer of Section 1.2 of the study protocol for the detailed study flow chart.



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled). These changes are not based on any unblinded study data.

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section. "Principal features of the analysis" encompass the confirmatory aspects of the trial, including the primary and key secondary endpoints/analyses, and the analysis populations associated with these analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	21-May-2015	To address the feedback from European health authority (EMA) on stratification for patients on medium and high doses of ICS to ensure that the benefit/risk is positive for both asthma populations.	The following text: Randomization will be stratified by age (<18 years, 18-64 years, ≥65 years), central eosinophil count (<150 cells/μL, 150 – 299 cells/μL, and ≥300 cells/μL) at screening and country. Was replaced with: Randomization will be stratified by age (<18 years, ~~18-64 years, ≥65 years~~≥18 years),

Amendment Number	Date Approved	Rationale	Description of statistical changes
			central eosinophil count (~~<150 cells/ µL, 150 – 299 cells/ µL, and~~ <300 cells/µL, ≥300 cells/ µL) at screening, ICS dose level (medium, high) and country.
4	21-Sep-2015	To address the feedback from European health authority (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA) not to pool the placebo arms	The following text was deleted: ~~The two placebo groups will be compared for the two primary efficacy endpoints: annualized rate of severe exacerbation events during the 52 weeks, and absolute change from baseline in FEV1 at Week 12. If they are similar for both endpoints based on the predefined criteria, the two placebo groups will be pooled together and all efficacy analyses will be performed with the pooled placebo group. The criteria to determine if the two placebo groups are similar will be specified in the SAP prior to database lock.~~
4	21-Sep-2015	To further meet the recommendation from EMA on stratification for patients on medium and high dose ICS to ensure that the benefit/risk is positive for both asthma populations, in addition to the added stratification factor of ICS dose level (medium, high).	The following text was added: The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized.
4	21-Sep-2015	To meet the request from Food and Drug Administration (FDA) to control overall type I error rate at a 2-sided alpha of 0.05.	The following text was deleted: ~~The secondary endpoints will be tested follow the predefined hierarchical order for the dose that meets the statistical significance for both primary endpoints: annualized event rate of severe exacerbation and absolute change from baseline in FEV1 at Week 12.~~ ~~The primary family error rate will be controlled at 2-sided 5% level for 2 primary endpoints and 2 doses. The family error rate will be controlled at 2-sided 5% level for primary and secondary endpoints within the dose group. The overall family error rate will be controlled at 1-sided 5% level for all endpoints across dose groups.~~ The following text was added: If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a

Amendment Number	Date Approved	Rationale	Description of statistical changes
			hierarchical testing procedure at a 2-sided 5% significant level. The first four tests will be 1) % change from baseline in FEV1 at Week 12 for 300 mg q2w versus placebo 2) absolute change from baseline in AQLQ global score at Week 12 for 300 mg q2w versus placebo 3) % change from baseline in FEV1 at Week 12 for 200 mg q2w versus placebo, 4) absolute change from baseline in AQLQ global score at Week 12 for 200 mg q2w versus placebo. The remaining list of secondary endpoints to be tested in the hierarchical order will be specified in SAP. The overall familywise error rate will be strongly controlled at a 2-sided 5% level for all tested endpoints across dose groups.
4	21-Sep-2015	To meet the request from Food and Drug Administration (FDA) to include treated but not randomized patients in the safety population	The following text: The analysis population for the safety endpoints will be the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received. Was replaced with: The analysis population for the safety endpoints will be the safety population, defined as all ~~randomized~~ patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received.
7	9-Aug-2016	To meet the request from FDA to provide data on patients treated with dupilumab manufactured with the intended commercial process	In order to have additional patients treated with dupilumab manufactured using the intended commercial process, more patients may be randomized than the originally planned sample size (1638) .
7	9-Aug-2016	Examine if inclusion of the loading dose impacts duration of sustained efficacy with regard to exacerbations	Additional analysis to assess the sustained treatment effect was added.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This section summarizes major changes in statistical analysis features made in approved SAP versions from statistical considerations in protocol or previous SAP versions, with emphasis on changes after study start (after the first patient was enrolled). These changes are made before database lock.

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	24-Jun-2016	Expand the multiplicity control procedure for additional secondary endpoints, sub-populations.	The testing order of secondary endpoints was expanded from protocol, and the complete list of endpoints to be tested in the hierarchical order was specified in Table 6
1	24-Jun-2016	To be aligned with protocol amendment 07	Anti-dupilumab antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 64 will be provided.
1	24-Jun-2016	To meet the request from FDA to assess any potential confounding effects of the loading dose on efficacy.	Sensitivity analyses were added to examine if the treatment effect of dupilumab is sustained throughout the 52-week treatment period or if there is any confounding effect of the use of the loading dose resulting in a larger treatment effect in the early part of the study. Annualized rates of severe exacerbation will also be analyzed versus placebo excluding efficacy data obtained during the first 4 weeks and 12 weeks of treatment of dupilumab/placebo respectively.
1	24-Jun-2016	To meet the request from FDA to provide data on patients treated with dupilumab manufactured with the intended commercial process	In order to have additional patients treated with dupilumab manufactured using the intended commercial process, more patients may be randomized than the originally planned sample size (1638). The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) complete Week 52 visit or discontinue from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR. Additional data between database lock and last patient completing last visit will be summarized in CSR addendum.
2	This version	The analyses for the intended commercial manufacture process will be specified in a separate SAP	Analyses of PK and FEV1 for the intended commercial manufacture process are removed from Section 2.4.4.1.2 and Section 2.4.6.1.1 in this

SAP version number	Date approved	Rationale	Description of statistical changes
			SAP
2	This version	Expand the multiplicity control procedure for additional secondary endpoints	Exacerbation requiring hospitalization or ER visit is added in the hierarchy of the multiplicity control procedure in Section 2.4.4.3
2	This version	Add analysis for severe exacerbation events resulting in hospitalization or ER visit.	The endpoint, Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit, is added in Section 2.1.3.2.2.2
2	This version	To solve the potential for non-convergence in the analysis of exacerbation event	Procedures of model handling are added when GLIMMIX procedure fails to achieve convergence in Section 2.4.4.1.1.
2	This version	Include multiple imputation in the sensitivity analysis of severe exacerbation per FDA feedback	PMM, control based PMM and tipping point analysis for severe exacerbation events are updated in Section 2.4.4.1.1.
2	This version	To solve the potential for non-convergence in MMRM models	Alternative model specification is added when MMRM model fails to achieve convergence in Section 2.4.4.1.2
2	This version	To add additional subgroup analysis and update subgroup definition based on characteristics of patient population.	Additional subgroup analysis based on Ethnicity (Hispanic, non-Hispanic) and baseline weight (<60kg, >=60kg) are added, definition of subgroups based on background controller medications are updated, subgroup with Baseline BMI<30 is split into two subgroups (<25, 25-<30) in Section 2.4.4.1.1.
2	This version	To obtained group-level estimate of post-bronchodilator FEV1 slope in treatment arm	Baseline by time interaction is removed from the mixed-effects model for post-bronchodilator FEV1 in Section 2.4.4.2.1
2	This version	To include additional handling of missing data in ACQ07	Spirometry data from the same day will be used to impute the 7th question if the value is missing in Section 2.5.3
2	This version	To be consistent with ISS SAP	The definition of AESI and selected AE groupings are updated in Section 2.1.4.1.
2	This version	To include combined PCSA criteria for adult and adolescence.	PCSA criteria in *Appendix A* are updated
2	This version	To be aligned with protocol amendment 07	Change from baseline in Health care resource utilization at Week 4 and 8 are removed in Section 2.1.3.2.2.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value of efficacy parameters is defined as the last available value up to randomization but prior to the first dose of study medication unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP). The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the patient is treated, or the last available value up to randomization if the patient is not exposed to IMP.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the post-baseline summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are

- Gender (Male, Female),
- Race (Caucasian/white, Black/of African descent, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other)
- Age in years (quantitative and qualitative variable : <18, 18-64, 65–74, 75-84, and ≥85 years)
- Ethnicity (Hispanic, non-Hispanic)
- Region (Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia, Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA)
- Territory (North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain and United Kingdom; Rest of World: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey and Ukraine)
- Weight in kg (quantitative and qualitative variable : <50, 50-<100 and ≥100 kg)
- BMI in kg/m2 (quantitative and qualitative variable: <30, ≥30 kg/m2)
- Alcohol drinking frequency (Never, At least monthly, At least weekly and At least daily) and number of standard alcohol drinks on a typical day when drinking (1 OR 2, >2)

Medical or surgical history

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

This 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.

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 polyposis history (Yes, Ongoing condition)
- Eosinophillic esophagitis history (Yes, Ongoing condition)
- Food allergy history (Yes, Ongoing condition)
- Hives history (Yes, Ongoing condition)

A patient is considered to have atopic medical condition if he/she has any of the following: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥100 IU/mL and at least one aeroantigen specific IgE is positive (≥0.35 IU/mL) at baseline.

Disease characteristics at baseline

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

- ICS dose level (medium, high as defined in Appendix C)
- Age of asthma onset
- Time since first diagnosis of asthma (years)
- Smoking history (Never, Former*), time since cessation of smoking (months) and smoking quantity in pack-years for former smokers

  * *Current smokers are excluded from this study.*
- Time since last severe asthma exacerbation (months)
- Number of severe asthma exacerbation experienced within1 year before Visit 1 (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥4)
- Eosinophil stratum at randomization (<0.3, ≥0.3 Giga/L)

- Baseline spirometry data including pre-bronchodilator FEV1 (L), percent predicted FEV1, post-bronchodilator FEV1 (L) and FEV1 reversibility (%).
- AM and PM PEF (L/min)
- AM and PM symptom scores
- Number of nocturnal awakenings/night
- ACQ-5 score
- ACQ-7 score
- AQLQ global score
- Number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol per day
- Hypersensitivity to aspirin/NSAID (Yes, Ongoing condition)

Severe asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma. Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken within 30 days before screening and until the end of the study, including asthma controller medications, systemic corticosteroids are to be reported in the case report form 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 first IMP injection. Prior medications can be discontinued before 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 until rollover to the LTS12551 study. A given medication can be classified as a prior medication, concomitant medication and posttreatment medication at the same time.
- Posttreatment medications are those the patient took in the period from the last administration of IMP + 99 days to the end of the study

2.1.2.1 Inhaled corticosteroid 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. The controller drugs will not be dispensed or supplied by the sponsor, but the sponsor will reimburse investigators for patients' use of controller drugs in the study to ensure all patients have access to their controllers.

Prior to screening, patients must be on a stable background therapy of a medium to high dose of ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a

maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc) for at least 3 months at a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months at a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are excluded). If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in Appendix C. The minimum daily dose of fluticasone propionate is 500 mcg (≥250 mcg of fluticasone propionate twice daily), which is equal to the upper limit of medium daily dose for fluticasone propionate as instructed in Appendix C. For ICS other than fluticasone propionate, please refer to the table in Appendix C which indicates the upper limit of the medium daily dose for each ICS which is equivalent to 500 mcg/day of fluticasone propionate. A list of recognized controller medications is provided in Appendix B. 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.

During the randomized treatment period, patient will continue to take their controller medication(s) used during the screening period. The dose and regimen should not be changed. Only a transient increase in dose of ICS in addition to other rescue medication will be allowed to treat acute symptoms of asthma as per investigator's guidance.

Upon completing the 52-week randomized treatment period, controller medication regimen for patients not continuing with the open label extension could be adjusted based on the investigator’s medical judgment. .

2.1.2.2 Reliever medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol 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 number of puffs as shown on the following table:

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
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 ->12 puffs.

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
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 ->12 puffs.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Baseline for efficacy endpoints is defined as the last non-missing value up to randomization but prior to the administration of the first IMP unless otherwise specified.

2.1.3.1 Primary efficacy endpoint(s)

There are two primary endpoints for this study, the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and the absolute change from baseline in pre-bronchodilator FEV1 at week 12.

A severe exacerbation event during the study is defined as a deterioration of asthma requiring:

- Use of systemic corticosteroids for ≥3 days; or
- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids

Two events are considered as different if the start dates are separated by at least 4 weeks.

The annualized rate of severe exacerbation events during the 52-week treatment period is defined as the number of severe exacerbation events with onset during the 52-week treatment period per patient-year. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and their additional off-treatment severe exacerbation events up to Visit 18(Week 52) will be included.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary endpoint

The key secondary endpoint of this study is percent change from baseline in pre-bronchodilator FEV1 at Week 12.

2.1.3.2.2 Other secondary efficacy endpoints

The other secondary efficacy endpoints include:

- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 Giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 Giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 Giga/L
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients on high dose of ICS
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients on high dose of ICS
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients on high dose of ICS
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 Giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 Giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 Giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Percent change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Change from baseline in other lung function measurements (% predicted FEV1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period

- Time to first severe exacerbation event
- Time to first loss of asthma control event (LOAC)
- Change from baseline in Asthma Control Questionnaire (ACQ)-5 score and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:
  - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)
  - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 12, 24, 36, and 52
- Change from baseline in PROs at Week 12, 24, 36, and 52:
  - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)
  - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L)
  - Hospital Anxiety and Depression Scale (HADS)
  - 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis
  - Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis

Endpoints to be formally tested with multiplicity adjustments are listed in the testing order in Section 2.4.4.3 and Table 6.

2.1.3.2.2.1 Annualized rate of loss of asthma control (LOAC) event

LOAC event during the study is defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days or
- ≥20% decrease in pre-bronchodilator FEV_1 compared to baseline or
- Increase in ICS dose ≥4 times than the dose at Visit 2 or
- A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to randomization (Day1); or
- Severe exacerbation event

The annualized rate of LOAC events during the 52-week treatment period is defined as the number of LOAC events with onset during the 52-week treatment period per patient-year.

2.1.3.2.2.2 Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit

Annualized rate of severe exacerbation event requiring hospitalization or emergency room visit (requiring systemic corticosteroids) during the 52-week treatment period and annualized rate of severe exacerbation event requiring hospitalization during the 52-week treatment period will also be analyzed.

2.1.3.2.2.3 Time to first severe exacerbation event/first LOAC event

If a patient has an event during the 52-week treatment period, regardless the patient is on the study treatment or discontinues the study treatment but remains in the study, the time to first severe exacerbation event/first LOAC event is defined as (onset date of the first severe exacerbation/LOAC event – randomization date +1).

If a patient has no severe exacerbation event/LOAC event during the study up to Visit 18/Week 52, then the patient will be considered as free of event until the date of visit at Visit 18 or the last contact date, whichever happens earlier.

2.1.3.2.2.4 Disease-specific efficacy measures

2.1.3.2.2.4.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (1). For pre-bronchodilator measured parameters, including FEV1, PEF, FVC and FEF 25-75%, spirometry will be performed after a wash out period of bronchodilators according to their duration of action, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

At least three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable and/or acceptable maneuvers, an explanation should be recorded. The largest FEV1 and largest FVC will be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve. The FEF 25-75% should be obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV1 (best test).

Japanese Respiratory Society predicted set are used for Japanese patients to calculated percent predicted FEV1 and NHANES III predicted set for all other patients.

2.1.3.2.2.4.2 Reversibility

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive two to up to four puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. Alternatively and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. FEV1 reversibility is calculated as Post-bronchodilator FEV1 - Pre-bronchodilator FEV1 and percent FEV1 reversibility is calculated as (Post-bronchodilator FEV1 - Pre-bronchodilator FEV1) / Pre-bronchodilator FEV1 * 100.

2.1.3.2.2.4.3 Post-bronchodilator (Post-BD) FEV1

Post-BD FEV1 is obtained from the spirometry performed after administration of reliever medications for reversibility test. The largest FEV1 will be recorded after the data are examined from all of the acceptable curves.

2.1.3.2.2.4.4 ACQ (Asthma Control Questionnaire)

The ACQ was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

2.1.3.2.2.4.4.1 ACQ-7 (Asthma Control Questionnaire, 7-question version)

The ACQ-7 has 7 questions- the first 5 items assess the most common asthma symptoms: 1. frequency in past week awoken by asthma during the night, 2. severity of asthma symptoms in the morning, 3. limitation of daily activities due to asthma, 4. shortness of breath due to asthma and 5. wheeze, plus 6. short-acting bronchodilator use and 7. FEV1 (pre-bronchodilator % predicted). 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).

Clinic staff scores the FEV1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 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 reflecting inadequately controlled asthma. On the 7-point scale of the ACQ-7, a change or difference in score of 0.5 at patient level 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 (2), any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing score, it will be 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.

2.1.3.2.2.4.4.2 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 is short version of ACQ-7, and ACQ-5 score is the mean of the first 5 questions of ACQ-7 and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). The last two questions on the ACQ-7, assessing lung functions, are not included in ACQ-5. 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 at patient level is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Missing scores will be handled in the same way as for ACQ-7 score.

2.1.3.2.2.5 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
- Respond to the morning and evening asthma symptom scale questions
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
- Record the number of nocturnal awakenings due to asthma symptoms

2.1.3.2.2.5.1 Morning (AM) and Evening (PM) Peak expiratory flow (PEF)

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 10 AM) prior to taking any albuterol or levalbuterol
- PM PEF performed in the evening (between 5:30 PM and 10 PM) prior to taking any albuterol or levalbuterol
- Patients should try to withhold albuterol or levalbuterol 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 in the 7 days prior to randomization including the morning diary completed on the randomization day prior to the first administration of IMP, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the randomization. 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. Calculation of periodical average of post-baseline AM/PM PEF is specified in Section 2.5.2.

2.1.3.2.2.5.2 Asthma Symptom Score Numerical Rating Scale (NRS)

Patients will record overall symptom scores in an electronic diary twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Symptoms experienced during the night will be recorded upon arising (AM symptom score). The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. Calculation of periodical average of post-baseline AM/PM symptom score is specified in Section 2.5.2.

2.1.3.2.2.5.3 Use of rescue/reliever medicine

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the patients in an electronic diary/PEF meter. In the case that Nebulizer solutions are used as an alternative delivery method, the nebulizer dose will be converted to number of puffs according to Section 2.1.2.2. Each patient should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically. The baseline number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day will be based on the mean of the 7 days prior to randomization.

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The baseline reliever med use will be calculated as follows: The mean of reliever puffs taken in each of the 7 diary days (minimum 4 diary days) prior to randomization, including the diary day that ends with the morning diary completed on the randomization day. A diary day cannot be included in the calculation if it is not complete, meaning if an evening or morning diary is missing for that diary day. Out of the 7 diary days, if less than 4 are incomplete, the baseline reliever use is the mean of reliever puffs in each of the complete dairy days. If 4 or more diary days are incomplete, the baseline reliever use is the mean of reliever puffs taken in the closest 4 diary days with complete reliever use information prior to randomization. Calculation of periodical average of post-baseline use of reliever puffs is specified in Section 2.5.2.

2.1.3.2.2.6 Patient-reported outcomes

2.1.3.2.2.6.1 Asthma Quality of Life Questionnaire) Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)

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

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental Stimuli (4 items)

Individual items are equally weighted. The overall score is the mean of response to each of the 32 questions. The score of each domain is the mean of response to each of the questions in that domain. The overall score and domain scores ranges from 1 to 7. Higher scores indicate better quality of life.

To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For the symptoms and activity limitation domain score, only one missing value per domain is acceptable. For the emotional function and environmental stimuli domain scores, no missing value is acceptable. For responses with more than acceptable amount of missing value(s), the overall or the domain score will be considered as missing. For responses with amount of missing value(s) within accept range, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ.

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The patient level MCID for AQLQ(S) is 0.5 (3).

2.1.3.2.2.6.2 22-item Sinonasal Outcome Test in those patients comorbid with bilateral nasal polyposis and/or chronic rhinosinusitis

SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis with or without nasal polyposis on health-related quality of life (see Appendix H). The SNOT-22 has 22 items, 5 domains and a global score. The 5 domains include Nasal (range 0-30), Ear (range 0-15), Sleep (0-20), General and Practical (0-30), and Emotional (0-15). The range of the global score is 0-110. Lower scores indicate less impact and the recall period is past 2 weeks. The domains and the items in each domain are as follows:

- Nasal: item 2, 3, 4, 6, 7, 12
- Ear: item 8, 9, 10

- Sleep: item 13, 14, 15, 16
- General and Practical: item 1, 5, 11, 17, 18, 19
- Emotional: item 20, 21, 22

The global score is the sum of response to each of the 22 questions. For responses with some item scores are missing, the global score will be imputed as mean of the completed scores × 22, providing at least 50% of items have been completed. If more than 50% of items are missing, the global score is set to missing. The score for each domain is the sum of response to each question in that domain. Missing score will be imputed as mean of the completed items in that domain × total number of items in that domain, providing at least 50% of items in that domain have been completed. If more than 50% of items in a domain are missing, the score for that domain is set to missing.

2.1.3.2.2.6.3 Hospital Anxiety and Depression Scale

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales (see Appendix I). The instrument is comprised of 14 items: 7 related to anxiety and 7 to depression. Each item on the questionnaire is scored from 0-3. The anxiety/depression score is the sum of the scores of the 7 related items; one can score between 0 and 21 for either anxiety or depression. And the total score is the sum of the scores of the 14 items ranging from 0-42.

The HADS was found to perform well in assessing anxiety disorders and depression in both somatic and psychiatric cases and (not only in hospital practice for which it was first designed) in primary care patients and the general population (4).

2.1.3.2.2.6.4 EQ-5D-5L

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (5). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system and the EQ VAS (see Appendix J). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. EQ-5D-5L health status will be converted into a single index value by using EQ-5D-5L value sets based on UK population. The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

2.1.3.2.2.6.5 Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))+12 in those patients with comorbid allergic rhinitis.

RQLQ(S)+12 (see Appendix K) is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: 1. Activities (3 items), 2. Sleep (3 items), 3. Non-nose/eye Symptoms (7 items), 4. Practical Problems (3 items), 5. Nasal Symptoms (4 items), 6. Eye Symptoms (4 items) and 7. Emotional (4 items). The RQLQ(S)+12 responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Individual items within the RQLQ(S)+12 are equally weighted. The overall score is calculated as the mean score of all items. And the score for each domain is calculated as the mean score of the items in each of the domains. No interpolation will be performed for missing scores. Higher scores indicated more health-related quality of life impairment (lower scores better). The instrument takes approximately 7 minutes to complete. An MID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (6).

2.1.4 Safety endpoints

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.

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 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 LTS12551 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 LTS12551 study.
- The treatment-emergent adverse event period will include both **treatment** and **residual treatment** epochs.
- 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 with pre-specified monitoring).

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 with pre-specified monitoring).

2.1.4.1 Adverse events variables

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 first administration of IMP
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period

All adverse events (including serious adverse events and adverse events with pre-specified monitoring/of special interests) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) 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 in Table 3:

Table 3 - Criteria for adverse events of special interest and other selected AE groupings

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1*): 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)

AE Grouping	Criteria
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
Other selected AE grouping	
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)
Hypereosinophilia	HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'

In addition, AESIs reported by the investigator in CRF will be summarized separately.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death poststudy: deaths occurring after the end of the study

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed in standard international units and international units will be used in listings and tables. The same set of analysis will also be prepared in US units.

Blood samples for clinical laboratories will be taken at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 12 (Week 28), Visit 13 (Week 32), Visit 14 (Week 36), Visit 15 (Week 40), Visit 16(Week 44), Visit 17(Week 48), Visit 18(Week 52), Visit 19(Week 56), Visit 20(Week 60), Visit 21(Week 64) and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, red blood cell count, platelet count
  - **White blood cells**: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- 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, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), albumin
  - **Pregnancy test**: serum β-human chorionic gonadotropin (all female patients) will be performed at screening (Visit 1) in women of childbearing potential
  - **Hepatitis screen**: clinical laboratory testing at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study) add hepatitis screen including hepatitis B surface antigen (HBs Ag), hepatitis B Surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), In case of results showing HBs Ag (negative), HBs Ab (negative) and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the investigator believes the patient is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient is a false positive.
  - **Hepatitis B viral load** will be tested at Visit 2, then every 12 weeks until Visit 14 and end of treatment period for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.
  - **HIV screen**: anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study)
  - **Anti-nuclear antibody (ANA)** will be tested at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study)

    Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

- Serum immunoglobulins (limited to Visit 1(Week -4±1), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64)): quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA.

Urine samples will be collected as follows:

- **Urinalysis** (limited to Visit 1(Week -4±1), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64)): Urine dipstick analysis specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- A **urine dipstick pregnancy test** will be performed at Visit 2 prior to randomization and Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 12 (Week 28), Visit 13 (Week 32), Visit 14 (Week 36), Visit 15 (Week 40), Visit 16(Week 44), Visit 17(Week 48), Visit 18(Week 52),Visit 21(Week 64)

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured at screening (Visit 1) for all patients and will be measured throughout the study for adolescent patients. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

2.1.4.5 Electrocardiogram variables

One recording of a standard 12-lead ECG will be performed centrally at Visit 1(Week -4±1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64). At the post-randomization visits, ECGs will be performed prior to investigational product administration. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG. All ECG recordings will be centrally read by independent experts.

2.1.4.6 Physical Examination

Physical examinations will be performed at Visit 1(Week -4±1), Visit 11 (Week 24), Visit 18(Week 52), and Visit 21 (Week 64) including an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient's disease.

Refer to Section 1.2 Study Flow Chart for the schedule of physical examination performed throughout this study.

2.1.5 Pharmacokinetic variables

Predose serum dupilumab concentrations at Visit 2 (Day 1), dupilumab trough levels at Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52 and follow-up serum dupilumab at Week 56, Week 60, Week 64 will be provided.

2.1.6 Anti-drug antibody (ADA) variables

Anti-dupilumab antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 64 will be provided. Patients who discontinue early from treatment or patients who choose not to participate in the OLE study visit may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall clinical presentation at that time.

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-emergent ADA responses are further classified as Persistent, Indeterminate or Transient
   a) Persistent Response - defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.
   b) Indeterminate Response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
   c) Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

4. 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 (1,000 ≤ Titer ≤ 10,000)

- High (Titer > 10,000)

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

2.1.7 Pharmacodynamics/genomics endpoints

Eotaxin-3, eosinophil cationic protein (ECP), total IgE and Thymus and Activation-Regulated Chemokine (TARC) will all be assayed at Visit 2(Week 0), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36) and Visit 18(Week 52).

Periostin will be assayed at Visit 2(Week 0), Visit 4 (Week 4), Visit 8 (Week 12) and Visit 18(Week 52). And antigen-specific IgE panels will be collected at Visit 2(Week 0), Visit 8 (Week 12) and Visit 18(Week 52).

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

Exhaled nitric oxide will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 3 (Week 2),Visit 4 (Week 4), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 14 (Week 36), Visit 17(Week 48), Visit 18(Week 52), Visit 19(Week 56), Visit 20(Week 60), Visit 21(Week 64)

Pharmacogenetic testing is optional and voluntary. A separate written informed consent form must be signed before sampling. For those patients who signed the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as specified in the study flow chart, and these samples will be stored for future analysis.

2.1.8 Vaccine response

Subjects planning to receive vaccinations for tetanus (alone or combined), influenza, pneumococcus or meningococcus during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine: the first should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits. The details on the date(s) of vaccination and the specific vaccines that are administered, such as brand and antigenic strains, should be collected (see Appendix L).

2.1.9 Health economic endpoints

A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, school days loss, etc) will be administered at Visit 2 and every 4 weeks thereafter.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

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

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who did not complete the 52-week treatment as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Patients who withdraw from study prior to Week 52
- Patients who withdraw from study prior to Week 52 by main reason for study discontinuation.
- Patients who withdraw from study
- Patients who withdraw from study by main reason for study discontinuation
- Status at last study contact

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. This summary will be provided by treatment group and may also be further subgrouped by region/stratum as applicable.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, efficacy populations will be summarized by number of patients on the randomized population.

- Efficacy population: intent-to-treat (ITT) population

The analysis populations for safety, pharmacokinetics/pharmacodynamics will be summarized by number of patents on the safety population.

- Safety population
- PK population
- ADA population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

5. 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, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

6. A patient is dispensed an 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.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

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

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available

Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population, but will be included in the safety population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population as defined in Section 2.3.1.1.

2.3.1.1 Intent–to-treat population

The intent-to-treat population is the randomized population analyzed according to the treatment group allocated by randomization.

Patients will be analyzed in the treatment group to which they are randomized.

2.3.2 Safety population

The safety population is defined as:

- All patients who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment patients actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose group.
- For patients on placebo but accidentally exposed to the other placebo dose, the treatment group allocation for as-treated analysis will be the treatment as randomized.

- For patients on dupilumab but accidentally receive different treatment from the planned, the actual treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose group.

2.3.3 Population for pharmacokinetics/pharmacodynamics analyses

The **PK population** will consist of all patients in the safety population with at least one evaluable serum concentration data. Patients will be analyzed according to the treatment actually received.

ADA population will consist of all patients in the safety population who had at least one reportable ADA results (either 'ADA negative' or 'ADA positive') after first dose of the study treatment.

Biomarkers will be analyzed in the **exposed population**, consisting of patients in the safety population.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (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.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history will be summarized by treatment group 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. Atopic medical history will be summarized separately.

No statistical testing on demographic and baseline characteristic data will be performed.

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.

2.4.2 Prior or concomitant medications

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 first IMP to last IMP +14 days and concomitant medication received during first IMP to 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 300 q2w group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, inhaled corticosteroid in combination with other controllers and reliever medications will be summarized separately.

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor.

2.4.2.1 ICS in combination with other controllers

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

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 the dupilumab 300 q2w group.

The total daily dose of ICS in asthma controller medication at randomization will be classified as medium-dose or high-dose according to Appendix C. 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 4 and Table 5. The equivalent dose is determined based on the thresholds in Appendix C. After conversion, the total daily dose for inhaled corticosteroid will be calculated and classified as medium or high dose.

Table 4 – Equivalent dose for inhaled corticosteroids for adults and adolescents (≥ 12 years)

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

* Fluticason furoate (FF) dose >=200 mcg is converted to equivalent fluticasone propionate(DPI or HFA) dose of (FF dose +1)×2.5; FF dose <200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of FF dose ×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.

Table 5 – Equivalent dose of inhaled corticosteroid for adults and children (Japan)

Inhaled corticosteroid	Equivalent dose (mcg) to 400 Fluticasone propionate (DPI or HFA)
FLUTICASONE FUROATE	100
BECLOMETHASONE DIPROPIONATE -HFA	400
CICLESONIDE -HFA	400
BUDESONIDE-DPI	800
BUDESONIDE INHALATION SUSPENSION	1.0 mg
BUDESONIDE INHALATION SOLUTION	1000
MOMETASONE FUROATE-DPI	400

Adapted from Japanese Guideline for Adult Asthma 2014 and Japanese Guideline for Childhood Asthma 2014

Example: A patient received 400 mcg Beclomethasone dipropionate -HFA and 400 mcg Ciclesonide-HFA. They are both equivalent to 400 fluticasone propionate. The combined total daily dose is equivalent to 800 fluticasone propionate.

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

2.4.2.1.1 Compliance

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 with the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS component is same as or greater than the prescribed dose. Similarly, a patient is considered as compliant with all controller medication if the actual dose of each controller medication is same as or greater than the prescribed dose.

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

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

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

Duration of IMP exposure is defined as last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations (see Section 2.5.3 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). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

>0 and ≤2 weeks

>2 and ≤4 weeks

>4 and ≤8 weeks

>8 and ≤12 weeks

>12 and ≤16 weeks

…

….

>48 and ≤52 weeks

>52 weeks

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

2.4.3.2 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 that the patient was planned to take during the treatment epoch defined in Section 2.1.4.

Above-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a higher dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Under-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a lower dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with at least 1 above-planned dose administration will also be provided, as well as numbers and percentages of patients with 0, (0, 20%], and >20% under-planned dose administrations.

Cases of overdose (defined as at least twice the intended dose during an interval of less than 11 days) will constitute serious adverse events and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period

Primary statistical model (ITT analysis) and adjustment for covariates

The primary analysis of the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period is to assess the efficacy of dupilumab in an intention-to-treat setting. In this primary approach, off-treatment measurements of patients who prematurely discontinue treatment will be included for the analysis. Patients who permanently discontinue the study medication will be encouraged to return to the clinic for all remaining study visits. If a patient stays in study until the end of 52-week treatment period, all severe exacerbation events that happen up to Visit 18 will be included in the primary analysis, regardless if the patient is on treatment or not. And the observation duration is defined as from randomization to Visit 18. If a patient withdraws from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to Week 52. This estimand compares the rate of severe exacerbation for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (7).

The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the observation period defined above as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Treatment groups, region, baseline eosinophil strata and baseline ICS dose level will be treated as categorical variable. Age and number of severe exacerbation events within 1 year prior to the study will be treated as continuous variable. Severe asthma exacerbation event prior to the study is defined as treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once or hospitalization or emergency medical care visit for worsening asthma (as defined in section Section 2.1.1). Log transformed observation duration will be the offset variable.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and its matching placebo will be derived by testing each dupilumab group versus its matching placebo separately. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals will be derived from the negative binominal model. The event rate ratio of each dupilumab group and its matching placebo, two-sided 95% confidence interval of the rate ratio based on the negative binomial model and its p-value will be provided.

Based on EMEA feedback, the rate difference between each dupilumab group and its matching placebo, two-sided 95% confidence intervals of the rate difference and its p-value derived using delta method will also be provided as supportive information.

Sample SAS code can be found below:

```
proc glimmix data=event;
  class eosblgpn ics trt01pn cntygr1n;
  model numevents=trt01pn age eosblgpn ics cntygr1n asmanum
                  /offset=logdur dist=negbin link=log solution;
run;
```

If the model fails to achieve convergence, different estimation algorithms will be applied following the order: default→LAPLACE→QUAD(8). If the issue still exists, other handling may be considered. The adjustment will be added to the footnote of the corresponding outputs.

The gross estimated of annualized events rate will also be presented by each treatment group. Mean cumulative function plot will be provided for descriptive purpose.

Estimand of clinical efficacy of dupilumab versus placebo

An analysis to assess the efficacy of dupilumab if patients adhere to the treatment as directed is also specified. In this approach, off-treatment measurements of patients who prematurely discontinue treatment will be excluded from the analysis. A negative binomial model with the same set of covariates as specified in the primary analysis will be used. This model will include severe exacerbation events occurring during the treatment epoch as the response variable and the log transformed duration of the treatment epoch will be the offset variable. This approach defines the estimand to be the efficacy of dupilumab with treatment adherence (7).

Handling of missing data

If patients withdraw from the study before Visit 18 (Week 52), severe exacerbation events that may occur after study discontinuation will not be observed. These patients are considered as patients with missing data on severe exacerbation. Number of patients with missing data, reasons and timing for patient withdrawals will be summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics will be provided for patients with missing data and patients with complete data separately. Graphical summaries of the dropout patterns such as Kaplan-Meier plots of time to study discontinuation with different reasons of discontinuation may be provided to examine if there is any different missing pattern between treatment groups. In addition, following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model

- *Pattern mixture model* ***- multiple imputation (PMM-MI)***

  For each patient with missing data of severe exacerbation events, individual monthly event probability will be estimated using observed data with adjustment of the planned treatment

group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. And binary event will be imputed on monthly basis using multiple imputation.

- *Control-based PMM-MI*

For each patient with missing data of severe exacerbation events, individual monthly event probability will be estimated using observation in the matching placebo arms only, with adjustment of age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. And binary event will be imputed on monthly basis using multiple imputation.

- *Tipping point analysis*

For each patient with missing data of severe exacerbation events, the monthly event will be imputed in a similar fashion as PMM-MI based on various odds values. If the patient is on dupilumab, the predicted odds will be increased; if the patient is on Placebo, the predicted odds value will be decreased. The adjusted rate will then be used to impute the number of events that would occur during the missing observation period. A sequence of increasing/decreasing ratio will be used to generate different imputed datasets.

For each of the above methods, a negative binomial model will be fitted using each of the complete datasets composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 18 (Week 52). SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the analysis with each dataset using Rubin's formula.

More details of the imputation and analyses methods are provided in Appendix D.

Subgroup analyses

To assess consistency of treatment effects across the subgroup levels, subgroup analyses will be performed for the annualized rate of severe exacerbation event during the 52-week treatment period by:

- Age group: < 18, 18-64, ≥ 65 years; < 18 , ≥ 18 years
- Gender (Male, Female)
- Region (Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia , Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA)

- Territory (North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain and United Kingdom; Rest of World: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey and Ukraine)
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, all the other)
- Ethnicity (Hispanic, non-Hispanic)
- Baseline blood eosinophil level (≥ 0.3 Giga/L, <0.3 Giga/L; ≥ 0.15 Giga/L, < 0.15 Giga/L)
- Background ICS dose levels at randomization (medium, high)
- Background controller type at randomization (ICS and LABA only, ICS and LABA and Anti-leukotrienes only, Other; ICS, LABA and any third controller, Other)
- Baseline FEV1 (≤ 1.75, > 1.75 L)
- ACQ-5 (≤ 2, >2)
- Number of severe asthma exacerbation prior to the study as defined in Section 2.1.1 (1,>1)
- Baseline weight (< 70, ≥ 70 - < 90, ≥ 90 kg; <60, ≥ 60 kg)
- Baseline BMI (< 25, 25- <30, ≥ 30 kg/m^2)
- Smoking history (Former, Never)
- Atopic medical condition (Yes, No)
- Age of onset of asthma (<18, 18-40, >40 years)
- Baseline predicted FEV1% (<60%, 60%-90%)
- Baseline periostin(NG/ML) (< median, ≥ median)
- Baseline fractional exhaled nitric oxide (FeNO) (< 25, ≥25- < 50, ≥50 ppb)

Treatment by subgroup interaction and its p-value will be derived from a negative binomial model. This model will include the total number of events occurring during the observation period as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to the study, subgroup (if different than the aforementioned covariates) and treatment by subgroup interaction as covariates. Log transformed observation duration will be the offset variable. If quantitative treatment by subgroup interaction is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be performed to evaluate possible qualitative interaction. Summary statistics of severe exacerbations will be provided within each subgroup. Forest plot of relative risks and corresponding CIs and forest plot of risk differences and corresponding CIs comparing each dupilumab dose group vs. its matching placebo for the subgroups will be provided.

For local submission, efficacy analyses may be performed in specific countries/regions, eg, Japan.

Loading dose evaluation (Sustained treatment effect evaluation)

To examine if the loading dose has any confounding effect on annualized rate of severe exacerbation during the 52-week randomized treatment period, a sensitivity analysis for the annualized rate of severe asthma exacerbation will be performed. It will include severe exacerbation events occurring after the first four weeks and 12 weeks, respectively, and only on-treatment events will be included to avoid possible confounding effect due to off-treatment data. Due to potential insufficient number of events after excluding data from the first 12 week, two dupilumab groups will be combined and two placebo groups will be combined. Results of the sensitivity analysis will be compared to the result of on-treatment analysis including all on-treatment severe exacerbation events during the study.

2.4.4.1.2 Absolute change from baseline in pre-bronchodilator (pre-BD) FEV_1 at Week 12

Primary statistical model (ITT analysis) and adjustment for covariates

The primary analysis of change from baseline in pre-BD FEV1 at Week 12 is to assess the efficacy of dupilumab in a real-world setting. The absolute change from baseline in FEV1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline in pre-BD FEV1 values up to Week 12 as response variables, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value and baseline-by-visit interaction as covariates. Treatment groups, sex, region, baseline eosinophil strata, baseline ICS dose level, and visit will be treated as categorical variables. Age and height will be treated as continuous variable. For patients who discontinue the treatment before Week 12, they will be asked and encouraged to return to the clinic for all remaining study visit and the additional off study-treatment pre-BD FEV1 values measured up to Week 12 will be included in the primary analysis. For patients who withdraw from the study before Week 12, pre-BD FEV1 values will be missing after study discontinuation. No imputation will be performed for missing values in the primary analysis. This estimand compares the change from baseline in pre-BD FEV1 for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (7).

An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in pre-BD FEV1 at Week 12 will be derived from the mixed-effect model. Difference in LS mean change from baseline, the corresponding 95% CI and the p-value with Kenward-Roger adjustment will be provided for comparison for each dupilumab group against its matching placebo. In addition, descriptive statistics including number of patients, mean, standard error and LS mean of change from baseline will be provided.

A sample SAS code can be found below:

```
proc mixed data=adsd.adre method=reml;
      where paramcd='FEV1' and avisitn ge 3 and avisitn le 8 and ittfl='Y';
      class subjid sex eosblgpn ics trt01pn avisitn cntygr1n;
      model chg = trt01pn sex age height ics eosblgpn cntygr1n avisitn
trt01p*avisitn base base*avisitn/ddfm=kr residual;
      repeated avisitn/type=un subject=subjid;
      lsmeans trt01pn*avisitn /pdiff cl ;
     estimate '300 mg q2w vs Placebo 2ml q2w at Week 12 Visit 8'
     trt01pn 0 -1 0 1  trt01pn*avisitn   0 0 0  0
                                         0 0 0 -1
                                         0 0 0  0
                                         0 0 0  1/ cl;
run;
```

If MMRM model fails to achieve convergence due to complexity of model specification, we may add some procedures to handle this issue including: 1) using maximum likelihood estimation instead of restricted maximum likelihood method; 2) covariance structure selection to reduce the number of unknown parameters to be estimated, the path is UN→TOEPH→TOEP→AR(1)→CS. The adjustment will be added to the footnote of the corresponding outputs.

Estimand of clinical efficacy of dupilumab versus placebo

To assess the treatment effect when the patients adhere to the study treatment as directed, on-treatment pre-BD FEV1 measurements will be analyzed using the similar MMRM model as for the primary analyses, including same set of covariates and estimation algorithm. The model will include on-treatment change from baseline in pre-BD FEV1 values up to Visit 8 (Week 12) as response variables. A pre-BD FEV1 value is considered as on-treatment if it's measured before or on the last dose date + 14 days.

Sensitivity analyses with different censoring methods for pre-BD FEV1 potentially confounded by systemic corticosteroid use

In addition, two sets of sensitivity analyses with different methods of handling pre-BD FEV1 measurements confounded by the systemic corticosteroid use will be performed:

- Censoring method 1: pre-BD FEV_1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date + 14 days will be excluded in order to reduce the confounding effect of systemic corticosteroids
- Censoring method 2: All pre-BD FEV_1 measurements collected on and after first day of systemic corticosteroid use will be excluded.

The above two censoring methods will be applied to both primary analyses and on-treatment analysis. On-treatment analysis with data censoring method 1 will be used to provide treatment effect size estimates without confounding effect of systemic corticosteroid use.

Handling of missing data

If a patient misses scheduled pre-BD FEV1 measurement during the first 12-week treatment, or withdraws from the study before Visit 8 (Week 12), he/she will have missing pre-BD FEV1 data at some time points up to Week 12. Descriptive statistics of pre-BD FEV1 by visit up to Week 12 will be summarized for patients with some missing data and patients with complete data up to Week 12 separately. Number of patients with missing pre-BD FEV1, reasons and timing for missing pre-BD FEV1 will be summarized by treatment groups. In addition, following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model:

- *Pattern mixture model-multiple imputation (PMM-MI)*

  Missing pre-BD FEV1 values will be imputed multiple times with adjustment for covariates including treatment groups, baseline eosinophil groups, age, sex, height, region, baseline ICS dose level and reason of treatment discontinuation. Each of the complete datasets will be analyzed using the ANCOVA model with change from baseline in pre-BD FEV1 at Week 12 as the response variable, treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline pre-BD FEV1 value as covariates. Then the SAS MIANALYZE procedure will be used to generate statistical inference by combining results using Rubin's formula.

- *Control based PMM-MI*

  The analysis is similar as the standard PMM-MI described above, except that it assumes that after withdrawal from the study, patients from the dupilumab groups would exhibit the same future evolution of pre-BD FEV1 as patients on the placebo who were not exposed to dupilumab.

- *Tipping point analysis*

  First, missing values will be imputed by PMM-MI as illustrated above. The imputed values in placebo group will then be shifted by adding a sequence of positive values and the imputed values in dupilumab group will be shifted by subtracting a sequence of positive values. For each combination of the shift parameters, each of the imputed and shifted datasets will be analyzed with the ANCOVA model and their results will be combined using Rubin's formula to generate statistical inference. LS mean difference between dupilumab and placebo in change from baseline in pre-BD FEV1 at week 12 and the corresponding p-values will be provided for each combination of shift parameters.

  More details of the imputation and analyses methods are included in Appendix D.

Subgroup analysis

To assess the consistency treatment effects across the subgroup levels, subgroup analyses will be conducted for the change from baseline in pre-BD FEV1 at Week 12 with the same set of subgroups as defined for the annualized rate of severe exacerbation events. Treatment-by-subgroup interaction at Week 12 and its p-value will be derived from a MMRM model. The model will include change from baseline in pre-BD FEV1 values up to Week 12 as response variables,

and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value, baseline-by-visit interaction, subgroup (if different than the aforementioned covariates), subgroup-by-treatment interaction and subgroup-by-treatment-by-visit interaction as covariates. If quantitative treatment by subgroup interaction at Week 12 is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be used to test the qualitative interaction. Summary statistics of change from baseline in pre-bronchodilator FEV1 will be provided within each subgroup. Forest plot of LS mean difference and corresponding CIs comparing each dupilumab dose group vs. its matching placebo for the subgroups will be provided.

Distribution of change from baseline in pre-BD FEV1

Cumulative distribution function of change from baseline in pre-BD FEV1 at Week 12 and Week 52 will be presented.

For each subgroup, a MMRM model will be used to analyze change from baseline in pre-BD FEV1 at Week 12. Change from baseline in pre-BD FEV1 up to Week 12 will be included as response variable. Treatment groups, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value and baseline-by-visit interaction will be included as covariates. LS mean change from baseline in pre-BD FEV1 at Week 12 for each treatment group and LS mean difference in change from baseline in pre-BD FEV1 at Week 12 for each dupilumab treatment group compared to placebo will be derived from the MMRM model for each subgroup.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Absolute/percent change from baseline for continuous endpoints

The key secondary endpoint, percent change from baseline in pre-bronchodilator FEV1 at Week 12, will be analyzed in the same way as for change from baseline in FEV1 at Week 12, with the only difference that percent changes, instead of absolute changes, from baseline in FEV1 up to Week 12 will be included as the response variables. MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time-points. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

Change from baseline in ACQ-5 and AQLQ at Week 24 will be analyzed using MMRM including change from baseline up to Week 24 as response variables, regardless if the patient is on treatment or not when the endpoint is measured. The model will include treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value, and baseline-by-visit interaction as covariates. MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time-points. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

Change from baseline in other continuous endpoint at all time-points will be analyzed using MMRM model including measurements up to Week 52. The model will include change from baseline in the endpoint values from Week 2 to Week 52 as response variables, regardless if the patient is on treatment or not when the endpoint is measured, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value and baseline-by-visit interaction as covariates. Sex and baseline height will be included as covariates only in the models for spirometry parameters. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

For post-bronchodilator FEV1, the rate of change in FEV1 (termed as FEV1 slope) will be compared between each dupilumab dose against its matching placebo. Change from baseline in post-bronchodilator FEV1 after Week 4 and after Week 8 will be analyzed correspondingly using linear mixed-effects model with treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, time since randomization, and treatment-by-time interaction and baseline post-bronchodilator FEV1 as covariates.

In addition to the MMRM analyses for change from baseline in ACQ-5, ACQ-7 and AQLQ total score a responder analysis will also be performed for these endpoints at Week 12, 24, 36 and 52. For ACQ-5 score, a logistic regression model will be used to compare percentage of patients who reached MCID (responders) in each dupilumab dose group against its matching placebo at the time points aforementioned correspondingly. Patients with change from baseline in ACQ-5 $\leq$ -0.5 will be considered as responders. Patients with change from baseline in ACQ-5 >-0.5 or with missing value will be considered as non-responders. The model will include treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline ACQ-5 score as covariates. Odds ratio of being a responder comparing each dupilumab dose group to its matching placebo group will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided. Responder analysis for ACQ-7 and AQLQ global score will be performed in the same way. For ACQ-7, a patient is considered as a responder if change from baseline in ACQ-7 score $\leq$ -0.5, or as a non-responder if change from baseline in ACQ-7 score > -0.5 or missing. For AQLQ global score, a patient is considered as a responder if change from baseline in AQLQ global score $\geq$0.5, or as a non-responder if change from baseline < 0.5 or missing. ACQ-7 score will also be analyzed in adolescent patient population separately.

2.4.4.2.2 Annualized event rate

Annualized rate of loss of asthma control (LOAC) event and annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period will be analyzed in the similar method as for the annualized rate of severe exacerbation events using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed observation duration will be the offset variable.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and its matching placebo will be derived by testing each dupilumab group versus its matching placebo separately. The estimated event rate for each treatment group and its two-sided 95% confidence intervals will be provided. The event rate ratio of each dupilumab group and its matching placebo, two-sided 95% confidence intervals of the rate ratio and its p-value will also be provided.

2.4.4.2.3 Time to event variables

A Cox regression model will be used to assess treatment differences in time to events defined in Section 2.1.3.2.2.3.

The model will include the time to the first event as the dependent variable, and four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Hazard ratio will be estimated for pairwise comparison between each dose of dupilumab and its matching placebo. The Kaplan-Meier method will be used to derive the probabilities that a patient would experience events up to Week 12, 24, 36 and 52 per each treatment group. Kaplan-Meier curves will be generated; quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

Sample SAS codes can be found as below:

```
proc phreg data=timeto;
      class subjid eosblgpn ics trt01pn cntygr1n /param=GLM;
      model aval*CNSR(1) =trt01pn age eosblgpn ics cntygr1n asmanum;
      contrast '200 mg q2w vs Placebo rate ratio' trt01pn -1 0 1 0
      0/estimate=exp;
      contrast '300 mg q2w vs Placebo rate ratio' trt01pn 0 -1 0 1
      1/estimate=exp;
run;
```

2.4.4.3 Multiplicity issues

To strongly control the type-I error rate for the primary family (two primary endpoints and two doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300 mg q2w versus placebo, 2) absolute change from baseline in FEV1 at Week 12 for 300 mg q2w versus placebo, 3) annualized severe exacerbation rate for 200 mg q2w versus placebo, 4) absolute change from baseline in FEV1 at Week 12 for 200 mg q2w versus placebo.

If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The complete list of the endpoints with their testing order is specified in Table 6.

Table 6 – Hierarchical testing order

	Endpoints	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
Primary endpoints	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population	3	1
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population	4	2
Secondary endpoints	Percent change from baseline in pre-bronchodilator FEV1 at Week 12 - ITT population	11	5
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil >=0.15 Giga/L	12	6
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline eosinophil >=0.15 Giga/L	13	7
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil >= 0.3 Giga/L	14	8
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline eosinophil >= 0.3 Giga/L	15	9
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil <0.3Giga/L	16	10
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with high dose ICS at baseline	22	17
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with high dose ICS/LABA at baseline	23	18
	Change from baseline in AQLQ global score at Week 24 - ITT population	24	19
	Change from baseline in AQLQ global score at Week 24 - ITT population with baseline eosinophil >= 0.3 Giga/L	25	20
	Change from baseline in ACQ-5 score at Week 24 - ITT population	26	21
	Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week treatment period - ITT population	28	27
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline blood eosinophil <0.3 Giga/L	30	29

2.4.5 Analyses of safety data

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

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last available value before the first dose of IMP.
- 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 A)
- PCSA criteria will determine which patients had 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. Summaries will include the endpoint value and/or the worst on-treatment value. The endpoint value is commonly defined as the value collected at the end of treatment. If this value is missing, this endpoint value will be the closest value prior to the end of treatment epoch. The worst value is defined as the nadir and /or the peak post-baseline (up to the end of treatment epoch or EOT) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.3.

2.4.5.1 Analyses of adverse events

General information

The primary focus of adverse event reporting will be on treatment-emergent adverse events. 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 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. 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 300 mg q2w group.

Analysis of all treatment-emergent adverse events

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

- Overview of treatment-emergent adverse events, 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 treatment-emergent adverse events by primary system organ class, showing number (%) of patients with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary system organ class
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- Number (%) of patients experiencing treatment-emergent adverse event(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

- A listing of all treatment-emergent adverse events will be presented

Analysis of all treatment-emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- A listing of all treatment-emergent serious adverse events will be presented

Analysis of all treatment-emergent adverse event(s) leading to permanent treatment discontinuation or drug interruption

- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC and PT, showing number (%) of patients with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.

Analysis of adverse events of special interest (AESI) and other selected AE groupings

- All treatment-emergent adverse events, 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 prespecified 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 any specific TEAE adjusted by the exposure duration
- All of the specific TEAE, by PT, showing the number (%) of patients, sorted by decreasing incidence of PT
- Number of patients with any specific TEAE adjusted by the exposure duration at risk. For each specific TEAE, Kaplan-Meier estimates of cumulative incidence at Week 12, 24, 36 and 52 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough

- Number (%) of patients with injection site reactions by the related injection.
- Number (%) of patients with different number of injection site reactions.

Analysis of pretreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All serious pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to permanent treatment discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

If only a few patients have pretreatment adverse events leading to permanent treatment discontinuation, a listing will be presented instead of the summary table above.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, poststudy)
- Deaths in nonrandomized patients or randomized but not treated patients

- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC .
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

A listing of deaths will be provided.

2.4.5.3 Analyses of laboratory variables

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, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For each continuous parameters listed in Section 2.1.4.3, mean changes from baseline with the corresponding standard error will be plotted over time in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and 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, 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 postbaseline visit by baseline status will be displayed by treatment group for each parameter. The

proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT and AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) (time to first observation of ALT > 3 x ULN or total bilirubin > 2 x ULN, whichever comes first) will be analyzed using Kaplan-Meier estimates, presented by treatment group. Consideration should be given to the impact of the spacing of scheduled tests. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

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 ≥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.

Summarize the normalization by parameter (to ≤1 x ULN or return to baseline) of elevated liver function tests 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 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 >=0.5 Giga/L. Number (%) of patients with post-baseline peak blood eosinophil >= 1 Giga/L, >=3 Giga/L and >=5 Giga/L will also be summarized in each treatment group and by baseline blood eosinophil status (All, <0.5 Giga/L,>=0.5 Giga/L).

2.4.5.4 Analyses of vital sign variables

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

The incidence of PCSAs at any time during the treatment-emergent adverse event 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

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) 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 treatment-emergent adverse event 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

2.4.6 Analyses of pharmacokinetic and pharmacodynamics variables

2.4.6.1 Pharmacokinetic analyses

2.4.6.1.1 Analyses of serum concentrations of SAR231893 (REGN668)

Serum concentrations of SAR231893 (REGN668) will be summarized in the PK population using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time. 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 lower limit of quantification (LLOQ), one-half of the LLOQ 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 plasma concentration considered equal to 0.

2.4.6.1.2 Analyses of ADA variables

The following summary will be provided based on 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, and patients with persistent, indeterminate and transient ADA response
- Number (%) of patient with transient treatment-emergent ADA
- Number (%) of patients with persistent treatment-emergent ADA

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

Kinetics of treatment-emergent ADA response

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

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

Impact of ADA on PK

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and serum concentration of dupilumab may be explored for each dupilumab dose group. Plot of serum concentration of functional SAR231893 (REGN668) versus visit will be provided by ADA classifications for each dupilumab dose group. Individual patient plots of PK according to ADA status will be provided to determine which individuals may have had PK impacted by ADAs.

Association of ADA with clinical efficacy endpoints

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and following efficacy endpoints may be explored for each dupilumab dose group:

- Annualized rate of severe exacerbation events
- Change from baseline in Pre-BD FEV1

Association of ADA with clinical safety endpoints

Association of safety versus ADA status may be analyzed in the ADA population. The safety assessment may focus on the following events:

- Severe injection site reactions last longer than 24 hours or serious injection site reactions
- Hypersensitivity reactions (SMQ hypersensitivity narrow search and confirmed by medical review)

- Anaphylactic reactions (SMQ anaphylactic reaction narrow search)

In response to AESI like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgment of the medical investigator and/or medical monitor.

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent and treatment-boosted) and safety may be explored.

2.4.6.2 Pharmacodynamics/genomics analyses

All biomarkers listed in Section 2.1.6 will be summarized in the Exposed population defined as patients who actually received at least 1 dose or part of a dose of the IMP. Baseline values will be the last value collected prior to the first IMP. For randomized but not treated patients, baseline value will be the last value collected prior to the randomization. Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline will be summarized.

For all parameters including antigen-specific IgEs with a positive (≥0.35 IU/mL) incidence of greater than 25% at baseline, values at each visit, absolute change from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point. Values reported as below the LLQ (lower limit of quantitation) will be imputed as a value one half of the LLQ.

Number and percentage of patients with no positive (≥0.35 IU/mL) antigen-specific IgE result, with positive (≥0.35 IU/mL) result for only one antigen, and with positive (≥0.35 IU/mL) results for at least two antigens will be summarized by treatment group and time point. Same analysis will also be performed using LLQ as the threshold.

Summary plots (mean +/- standard error of the mean) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for each biomarker by treatment group.

Exploratory analysis of DNA/RNA will be addressed in a separate document.

2.4.7 Analyses of vaccine response

For patients who receive vaccination, vaccine IgG in serum prior and after vaccination will be summarized by treatment groups with descriptive statistics.

2.4.8 Analyses of health economics variables

Analyses of health care resource utilization will be performed under the responsibility of the Health Economics and Reimbursement Argumentation department of Sanofi. Methods and results will be made available in a separate report.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age is calculated as:

Integer part of (informed consent date -birth date)/365.25

Age of onset of asthma is calculated as:

Integer part of (asthma onset date - birth date)/365.25

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

(Year of randomization -Year of first diagnosis of asthma) + (month of randomization - month of first diagnosis of asthma)/12

Time since cessation of smoking is calculated as:

(Year of randomization - Year of cessation)×12 + (month of randomization -month of cessation)

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

(Year of randomization – Year of last asthma exacerbation)×12 + (month of randomization – month of last asthma exacerbation)

BMI is calculated as:

Weight in kg / (height^2 in meters)

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

Number of pack-year= (packs smoked per day) × (years as a smoker)

Renal function formulas

For patients ≥ 18 years old, creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault:

CLcr (ml/min) = (140 - age) × weight (kg) × (1 - 0.15 × sex (0-M, 1-F))/ (0.814 × creatinine (μmol/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:

Age = integer part of (lab sampling date - birth date)/365.25

For patients < 18 years old, CLcr value will be derived using the equation of GFR Bedside Schwartz

$$GFR\ (mL/min/1.73\ m2) = k \times height\ (cm) / sCr\ (mg/dL)] ,$$

Where the coefficient k=0.65 for adolescent male patients, or k=0.55 for adolescent female patients.

2.5.2 Data handling conventions for secondary 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, number of awakenings	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 113	86-113	85-112	Diary day 85-112
Day 141	114-141	113-140	Diary day 113-140
Day 169	142-169	141-168	Diary day 141-168

Time point	Morning PEF, asthma symptom score, number of awakenings	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Day 197	170-197	169-196	Diary day 169-196
Day 225	198-225	197-224	Diary day 197-224
Day 253	226-253	225-252	Diary day 225-252
Day 281	254-281	253-280	Diary day 253-280
Day 309	282-309	281-308	Diary day 281-308
Day 337	310-337	309-336	Diary day 309-336
Day 365	338-365	337-364	Diary day 337-364
Day 393	366-393	365-392	Diary day 365-392
Day 421	394-421	393-420	Diary day 393-420
Day 449	422-449	421-448	Diary day 421-448

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 dairy on day 14 and the morning dairy on day 15.

2.5.3 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 missing answer to the 7th question in ACQ-7

If the score is missing from the site report, the FEV1 % predicted value from spirometry test will be used to derive the 7th score. Only the spirometry performed on the same day when ACQ-7 is evaluated will be used. And if there are multiple FEV1% predicted values available on the same day, the lowest one will be used to score the 7th item. If the score of the 7th question is still missing but the questionnaire is complete at the prior visit, the missing score for the 7th question will be imputed as: (score of the 7th question at the prior visit) □ (sum of scores of the first six questions at the current visit) / (sum of scores of the first six questions at the prior visit). If the questionnaire from the prior visit is not complete either or if the ACQ-7 score at the prior visit is 0, which makes it infeasible to implement the algorithm, the missing score will be imputed as the average of the other six questions at the current visit. If scores of the first six questions are missing, then the ACQ-7 score for the current visit will be missing.

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 date/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 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; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥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.

2.5.4 Windows for time points

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP administration. Selected safety variables will be summarized by the analysis window define in Table 8 for the by visit descriptive analysis. All available values from central lab will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 8 – Time window for safety endpoints

		Time windows for							
Visit	**Target Day**	**Vital signs**	**ECG endpoints**	**Clinical lab testing**	**Serum Pregnancy test**	**Urine Pregnancy test**	**Urinalysis, Serum immunoglobulins**	**Hepatitis B viral load**	**Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy**
Visit 1 (Week -4±1)	-28±7	<-14	1-	<-14	1-		1-		1-
Visit 2 (Week 0)	1	-14-1-		-14-1-		1-		1-	
Visit 3 (Week 2)	15	1+-21	1+-21						
Visit 4 (Week 4)	29	22-35	22-56	1+-42		1+-42			
Visit 5 (Week 6)	43	36-49							
Visit 6 (Week 8)	57	50-63		43-70		43-70			
Visit 7 (Week 10)	71	64-77							
Visit 8 (Week 12)	85	78-98	57-126	71-98		71-98	1-126	1-126	
Visit 9 (Week 16)	113	99-126		99-126		99-126			

		Time windows for							
Visit	Target Day	Vital signs	ECG endpoints	Clinical lab testing	Serum Pregnancy test	Urine Pregnancy test	Urinalysis, Serum immunoglobulins	Hepatitis B viral load	Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy
Visit 10 (Week 20)	141	127-154		127-154		127-154			
Visit 11 (Week 24)	169	155-182	127-210	155-182		155-182	127-210	127-210	
Visit 12 (Week 28)	197	183-210		183-210		183-210			
Visit 13 (Week 32)	225	211-238		211-238		211-238			
Visit 14 (Week 36)	253	239-266	211-308	239-266		239-266	211-308	211-308	
Visit 15 (Week 40)	281	267-294		267-294		267-294			
Visit 16 (Week 44)	309	295-322		295-322		295-322			
Visit 17 (Week 48)	337	323-350		323-350		323-350			1+

		Time windows for							
Visit	Target Day	Vital signs	ECG endpoints	Clinical lab testing	Serum Pregnancy test	Urine Pregnancy test	Urinalysis, Serum immunoglobulins	Hepatitis B viral load	Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy
Visit 18 (Week 52)	365	351-378	309-406	351-378		351-406	309-406	>308	
Visit 19 (Week 56)	393	379-406		379-406					
Visit 20 (Week 60)	421	407-434		407-434					
Visit 21 (Week 64)	449	>434	>406	>434		>406	>406		

1^{-}: up to 1^{st} dose date/time; 1^{+}: after 1^{st} dose date/time;

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a patient receives IMP prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first IMP administration for that patient. For the primary analyses, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 9. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For the on-treatment sensitivity analyses, only scheduled measurements collected during the treatment epoch will be assigned to a time window.

Table 9 – Time window for efficacy variables

		Time windows for		
Visit	**Target Day**	**Pre-bronchodilator Spirometry, ACQ-5, ACQ-7**	**Post-bronchodilator spirometry, reversibility**	**AQLQ(S), EQ-5D-5L, HADS, SNOT-22, RQLQ(S)+12**
Visit 1 (Week -4±1)	-28±7	<-14		
Visit 2 (Week 0)	1	-14-1^{-}	1^{-}	1^{-}
Visit 3 (Week 2)	15	1^{+}-21	1^{+}-21	
Visit 4 (Week 4)	29	22-35	22-42	
Visit 5 (Week 6)	43	36-49		
Visit 6 (Week 8)	57	50-63	43-70	
Visit 7 (Week 10)	71	64-77		
Visit 8 (Week 12)	85	78-98	71-126	1-126
Visit 9 (Week 16)	113	99-126		
Visit 10 (Week 20)	141	127-154		
Visit 11 (Week 24)	169	155-182	127-210	127-210
Visit 12 (Week 28)	197	183-210		
Visit 13 (Week 32)	225	211-238		
Visit 14 (Week 36)	253	239-266	211-308	211-308
Visit 15 (Week 40)	281	267-294		
Visit 16 (Week 44)	309	295-322		
Visit 17 (Week 48)	337	323-350		
Visit 18 (Week 52)	365	351-378	309-406	309-406
Visit 19 (Week 56)	393	379-406		
Visit 20 (Week 60)	421	407-434		
Visit 21 (Week 64)	449	>434	>406	>406

1^{-}: up to randomization and before 1st dose date/time; 1^{+}: after randomization or 1st dose date/time

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP administration if the patient is treated with study treatment, or the randomization date if the patient is not treated. Pharmacokinetics /pharmacodynamics variables will be summarized by the analysis window defined in Table 10 for the by visit descriptive analyses. All available values of measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 10 – Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target day	Time windows for					
		Eotaxin-3, ECP, total IgE, TARC	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Antigen-specific IgE	Periostin
Visit 1 (Week -4±1)	-28±7		<-14				
Visit 2 (Week 0)	1	1-	-14-1-	1-	1-	1-	1-
Visit 3 (Week 2)	15		1+-21	1+-21			
Visit 4 (Week 4)	29		22-56	22-42			1+-56
Visit 5 (Week 6)	43						
Visit 6 (Week 8)	57			43-70			
Visit 7 (Week 10)	71						
Visit 8 (Week 12)	85	1+-126	57-98	71-98	1-126	1-126	57-224
Visit 9 (Week 16)	113		99-126	99-140			
Visit 10 (Week 20)	141		127-154				
Visit 11 (Week 24)	169	127-210	155-210	141-210	127-266	127-266	
Visit 12 (Week 28)	197						
Visit 13 (Week 32)	225						
Visit 14 (Week 36)	253	211-308	211-294	211-308			
Visit 15 (Week 40)	281						
Visit 16 (Week 44)	309						
Visit 17 (Week 48)	337		295-350				
Visit 18 (Week 52)	365	>308	351-378	309-378	267-406	>267	>224
Visit 19 (Week 56)	393		379-406	379-406			
Visit 20 (Week 60)	421		407-434	407-434			
Visit 21 (Week 64)	449		>434	>434	>406		

Visit	Target day	Time windows for					
		Eotaxin-3, ECP, total IgE, TARC	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Antigen-specific IgE	Periostin

1-: up to 1st dose date/time or randomization if patient is not treated; 1+: after 1st dose date/time or randomization date if patient is not treated;

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries, computation of baseline, worst values, and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Due to the large number of centers, the randomization is stratified by country. Due to small sample size in some countries, the countries will be pooled into regions as defined below for the analyses:

- East Europe: Hungary, Poland, Russia, Turkey and Ukraine
- Western Countries: Australia , Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA
- Asia: Japan, South Korea and Taiwan;
- Latin America: Argentina, Brazil, Colombia, Chile and Mexico

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) complete Week 52 visit or discontinue from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR. Additional data between database lock and last patient completing last visit will be summarized in CSR addendum.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

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